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Visual cycle modulators versus placebo or observation for the prevention and treatment of geographic atrophy due to age-related macular degeneration (Review)

Yeong JL, Loveman E, Colquitt JL, Royle P, Waugh N, Lois N

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[Intervention Review]

Visual cycle modulators versus placebo or observation for the prevention and treatment of geographic atrophy due to age-related macular degeneration

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ABSTRACT

Background

Age-related macular degeneration (AMD) is a highly prevalent condition in an ever-increasing elderly population. Although insidious in the early stages, advanced AMD (neovascular and atrophic forms) can cause significant visual disability and economic burden on health systems worldwide. The most common form, geographic atrophy, has no effective treatment to date, whereas neovascular AMD can be treated with intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections. Geographic atrophy has a slow disease progression and patients tend to have preserved central vision until the final stages. This tendency, coupled with the use of modern imaging modalities, provides a large window of opportunity to intervene with validated methods to assess treatment efficacy. As geographic atrophy is an increasingly common condition with no effective intervention, many treatments are under investigation, one of which is visual cycle modulators. These medications have been shown to reduce lipofuscin accumulation in pre-clinical studies that have led to several clinical trials, reviewed herein.

Objectives

To assess the efficacy and safety of visual cycle modulators for the prevention and treatment of geographic atrophy secondary to AMD.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) (2020, Issue 1); MEDLINE Ovid; Embase Ovid; Web of Science Core Collection; Scopus; Association for Research in Vision and Ophthalmology (ARVO) website; ClinicalTrials.gov and the WHO ICTRP to 11 January 2020 with no language restrictions. We also searched using the reference lists of reviews and existing studies and the Cited Reference Search function in Web of Science to identify further relevant studies.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-randomised clinical studies (if available) that compared visual cycle modulators to placebo or no treatment (observation) in people diagnosed with AMD (early, intermediate or geographic atrophy).

Data collection and analysis

Two authors independently assessed risk of bias in the included studies and extracted data. Both authors entered data into RevMan 5. We resolved discrepancies through discussion. We graded the certainty of the evidence using the GRADE approach.

Main results

We included three RCTs from the USA; one of these had clinical sites in Germany. Two studies compared emixustat to placebo while the other compared fenretinide to placebo. All assigned one study eye per participant and, combined, have a total of 821 participants with a majority white ethnicity (97.6%). All participants were diagnosed with geographic atrophy due to AMD based on validated imaging modalities. All three studies have high risk of attrition bias mainly due to ocular adverse effects of emixustat and fenretinide. We considered only one study to be adequately conducted and reported with high risk of bias in only one domain (attrition bias). We considered the other two studies to be poorly reported and to have high risk of attrition bias and reporting bias.

People with geographic atrophy treated with emixustat may not experience a clinically important change in best-corrected visual acuity (BCVA) between baseline and 24 months compared to people treated with placebo (mean difference (MD) 1.9 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, 95% confidence interval (CI) -2.34 to 6.14, low-certainty evidence). Emixustat may also result in little or no difference in loss of 15 ETDRS letters or more of BCVA compared with placebo at 24 months (16.4% versus 18%) (risk ratio (RR) 0.91, 95% CI 0.59 to 1.4, low-certainty evidence). In terms of disease progression, emixustat may result in little or no difference in the annual growth rate of geographic atrophy compared with placebo (mean difference MD 0.09 mm²/year (95% CI -0.26 to 0.44, low-certainty evidence).

All three studies reported adverse events of both drugs (emixustat: moderate-certainty evidence; fenretinide: low-certainty evidence). The main adverse events were ocular in nature and associated with the mechanism of action of the drugs. Delayed dark adaptation (emixustat: 54.5%; fenretinide: 39.3%) and chromatopsia (emixustat: 22.6%; fenretinide: 25.2%) were the most common adverse events reported, and were the most prevalent reasons for study dropout in emixustat trials. These effects were dose-dependent and resolved after drug cessation. No specific systemic adverse events were considered related to emixustat; only pruritus and rash were considered to be due to fenretinide. One emixustat study reported six deaths, none deemed related to the drug.

None of the included RCTs reported the other pre-specified outcomes, including proportion of participants losing 10 letters or more, and mean change in macular sensitivity. We planned to investigate progression to advanced AMD (geographic atrophy or neovascular AMD) in prevention studies, including participants with early or intermediate AMD, but we identified no such studies.

Two of the included studies reported an additional outcome - incidence of choroidal neovascularisation (CNV) - that was not in our published protocol. CNV onset may be reduced in those treated with emixustat but the evidence was uncertain (risk ratio (RR) 0.67, 95% CI 0.27 to 1.65, low-certainty evidence), or fenretinide (RR 0.5, 95% CI 0.26 to 0.98, low-certainty evidence) compared to placebo. A dose-dependent relationship was observed with emixustat.

Authors' conclusions

There is limited evidence to support the use of visual cycle modulators (emixustat and fenretinide) for the treatment of established geographic atrophy due to AMD. The possible reduction in the incidence of CNV observed with fenretinide, and to a lesser extent, emixustat, requires formal assessment in focused studies.

PLAIN LANGUAGE SUMMARY

How effective are visual cycle modulators (a type of medicine) for preventing and treating geographic atrophy (a degenerative eye condition)?

Why is this question important?

Geographic atrophy is an eye condition that leads to progressive loss of central vision. It is an advanced form of age-related macular degeneration (AMD), a degenerative condition that usually develops in people over the age of 50. The condition affects the central part (macula) of the back of the eye (retina). There are two types of AMD: 'wet' and 'dry'. In wet AMD, blood vessels in the eye leak, whereas in dry AMD they do not. Geographic atrophy is a late stage of dry AMD.

Currently, we do not know how to prevent or treat vision loss caused by geographic atrophy. One potential treatment option is a type of medicine called a visual cycle modulator. Visual cycle modulators stop a toxic material (lipofuscin) from accumulating in the retina, and so they may be able to slow down vision loss in people with the condition.

We conducted a review of the evidence from research studies to find out about the benefits and risks of visual cycle modulators for treating and preventing geographic atrophy.

How did we identify and evaluate the evidence?

First, we searched for all relevant studies in the medical literature. We then compared the results, and summarised the evidence from all the studies. Finally, we assessed how certain the evidence was. To do this, we considered factors such as the way studies were conducted, study sizes, and consistency of findings across studies. Based on our assessments, we categorised the evidence as being of very low-, low-, moderate- or high-certainty.

What did we find?

We found three studies conducted in the USA and Germany that involved a total of 821 people with advanced dry AMD. All three studies were randomised controlled studies: clinical studies where people were randomly put into one of two or more treatment groups. Investigators

treated the participants for between 90 days and 24 months, and followed them for between seven and 30 days once treatment ended. The studies compared the effects of a placebo (dummy) treatment against two different visual cycle modulators: emixustat (2 studies) and fenretinide (1 study).

Emixustat against placebo

Low-certainty evidence suggested that there may be little to no difference between emixustat and placebo when considering:

- Average change in vision loss;
- The proportion of people who lost 15 letters or more according to a vision chart; or
- The progression of geographic atrophy.

Fenretinide against placebo

Low-certainty evidence suggested that geographic atrophy may progress at a slightly slower rate in people treated with fenretinide at a dose of 300 mg per day compared to a placebo. However, it was not clear whether this difference was important enough to make a difference to patients.

Adverse (unwanted) effects

Moderate- to low-certainty evidence suggested that:

- the most common adverse effects reported were delayed adaptation to darkness and visual disturbance (such as abnormally coloured vision, or darkened areas in the visual field). These effects increased with the size of dose of medicine, and disappeared once the treatment had ended.
- Emixustat was probably not associated with adverse effects other than problems that affected the eye (such as visual disturbance), or with serious adverse effects.
- Fenretinide may be associated with an itchy skin, or a rash.

What did we not find?

We did not find any studies that compared the effects of visual cycle modulators and placebo on:

- The proportion of people who lost 10 letters or more according to a vision chart;
- Average change in the macula's sensitivity to light; or
- Progression to advanced AMD in people with early- or intermediate-stage AMD.

What does this mean?

Our review of the evidence suggests that, in people with advanced AMD, visual cycle modulators may make little or no difference to:

- the progression of geographic atrophy; and
- vision loss.

Our confidence in these findings is low. The results of our review are likely to change if more evidence becomes available.

How-up-to date is this review?

The evidence in this Cochrane Review is current to January 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Emixustat compared to placebo for people with geographic atrophy due to AMD

Emixustat compared to placebo for people with geographic atrophy due to AMD

Patient or population: people with geographic atrophy due to AMD

Setting: Outpatient clinics

Intervention: Emixustat (2 mg once in the morning, 2.5 mg once in the morning, 5 mg once in the morning, 5 mg once in the evening, 7 mg once in the morning, 10 mg once in the morning)

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with emixustat				
Change in BCVA from baseline to 24 months*	The mean change in BCVA from baseline to 24 months* was -7.7 ETDRS letters	MD 1.9 ETDRS letters more (2.34 fewer to 6.14 more)	-	320 (1 RCT)	⊕⊕⊕⊕ LOW ^{a b}	* = or to last follow-up visit for participants withdrawing earlier.
Proportion of participants losing ≥ 15 EDTRS letters at 24 months**	Study population		RR 0.91 (0.59 to 1.40)	498 (1 RCT)	⊕⊕⊕⊕ LOW ^{b c}	** = Follow-up BCVA was taken 30 days after participants stopped taking the treatment assigned throughout the study period.
	180 per 1,000	164 per 1,000 (106 to 253)				
Proportion of participants losing ≥ 10 EDTRS letters**	Not measured		-	-	-	** = Follow-up BCVA was taken 30 days after participants stopped taking the treatment assigned throughout the study period.
Progression of geographic atrophy Follow up: range 6 months to 24 months	The mean progression of geographic atrophy was 1.69 mm ² /year	MD 0.09 mm ² /year more (0.26 fewer to 0.44 more)	-	503 (1 RCT)	⊕⊕⊕⊕ LOW ^{b d}	All available lesion areas collected over the 24 month study period for each treatment dose were utilised.
Progression to advanced AMD (geographic atrophy or neovascular)	Not measured		-	-	-	
Mean change in macular sensitivity	Not measured		-	-	-	

Adverse events	Ocular adverse events, specifically delayed dark adaptation (54.5%) and chromatopsia (22.6%) were the most common among emixustat-treated participants. These events were dose-dependent and resolved after drug cessation. Incidence of systemic adverse events reported among emixustat-treated participants (20.8%) were similar to placebo (22.6%).	-	575 (2 RCTs)	⊕⊕⊕⊖ MODER- ATE ^e	Number of systemic adverse events were not reported fully in Dugel 2015.
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***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AMD: Age-related macular degeneration; **BCVA:** Best-corrected visual acuity; **CI:** Confidence interval; **ETDRS:** Early Treatment Diabetic Retinopathy Study; **MD:** Mean difference; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence

High-certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate-certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low-certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low-certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

^a Downgraded for imprecision (-1): 95% confidence interval ranged from -2 to +6 ETDRS letters

^b Downgraded for risk of bias (-1): This trial had a high and unequal dropout rate. 80% of participants in the placebo arm completed the study whereas only 57% of participants combined from all three emixustat arms completed the study

^c Downgraded for imprecision (-1): 95% confidence interval for RR ranged from 0.59 to 1.4

^d Downgraded for imprecision (-1): 95% confidence interval ranged from -0.26 to 0.44 mm²/year

^e Downgraded for risk of bias (-1): Included trials were judged at risk of attrition bias

Summary of findings 2. Fenretinide compared to placebo for people with geographic atrophy due to AMD

Fenretinide compared to placebo for people with geographic atrophy due to AMD

Patient or population: people with geographic atrophy due to AMD

Setting: Outpatient clinics

Intervention: Fenretinide (100 mg and 300 mg--once a day dosage)

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with fenretinide				

Change in BCVA from baseline to 24 months		-	246 (1 RCT)	⊕⊕⊕⊖ LOW ^a	This outcome was reported only in a graphical format; numerical data were not provided. The corresponding author was contacted but he could not provide further details. Data points on the graph in the original published manuscript were not clear enough for us to extract data accurately to perform data analyses. The authors stated in their manuscript that there were no differences in mean ETDRS letter loss between the three groups at month 24, though the 300 mg group had lost more letters at 12 to 18 months. In addition, we were unsure if only participants who have completed at least 18 months of the study were included in this analysis as per the primary efficacy outcome measure of the progression rate of geographic atrophy lesion.
Proportion of participants losing ≥ 15 EDTRS letters	Not measured	-	-	-	
Proportion of participants losing ≥ 10 EDTRS letters	Not measured	-	-	-	
Progression of geographic atrophy Follow up: range 18 months to 24 months	The median growth rate in the fenretinide 100 mg arm was 2.14 mm ² /year (SD 1.66), fenretinide 300 mg arm was 1.95 mm ² /year (SD 1.22) and the placebo cohort was 2.03 mm ² /year (SD 1.24). Confidence intervals were not provided for these comparisons.	-	142 (1 RCT)	⊕⊕⊕⊖ LOW ^a	Treatment effect was difficult to calculate as the data was presented as median with standard deviation (mm ² /year). The corresponding author was contacted but he could not provide us with further details.
Progression to advanced AMD (geographic atrophy or neovascular)	Not measured	-	-	-	
Mean change in macular sensitivity	Not measured	-	-	-	
Adverse events	Ocular adverse events, specifically delayed dark adaptation (39.3%) and visual disturbance (25.2%) were the most common among fenretinide-treated participants. These events were dose-dependent and resolved after drug cessation. Fenretinide can also cause rash and pruri-	-	246 (1 RCT)	⊕⊕⊕⊖ LOW ^a	The reported systemic adverse events were not fully elaborated apart from rash and pruritus. There is also potential confounding effect as more participants in the 300 mg arm (81%) had geographic atrophy lesions that involved or encroached upon the fovea at baseline compared to those in the placebo arm (70%).

tus. 5 events were reported compared to 0 events in the placebo arm.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

GRADE Working Group grades of evidence

High-certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate-certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low-certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low-certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

^a Downgraded for risk of bias (-2): High drop-out rate in the fenretinide groups compared to placebo; 35% of fenretinide 100 mg and 31% of fenretinide 300 mg participants withdrew compared to the placebo treated participants (17%). Selective reporting of the efficacy of fenretinide and associated systemic adverse events.

BACKGROUND

Description of the condition

Age-related macular degeneration (AMD) is a progressive chronic disease of the central retina (macula), typically affecting the elderly population (Joachim 2015; Klein 2007). AMD is a condition with a continuous spectrum that can be classified into early, intermediate and advanced stages (Ferris 2013). Both early and intermediate stages are characterised by the presence and size of drusen and by the presence or absence of pigmentary changes in the macula (Ferris 2013). Patients tend to be asymptomatic during these early stages (Lim 2012). However, the central vision is severely affected as the condition progresses to advanced AMD, where geographic atrophy, or neovascular AMD (also known as exudative AMD), lead to the loss of photoreceptor cells (visual cells) and retinal pigment epithelium (RPE) at the macula. The severity of AMD is associated with increasing age, smoking, cardiovascular factors and genetics (Joachim 2015; Klein 2007; Lim 2012; Wong 2014).

Geographic atrophy is the most prevalent form of advanced AMD (Petrukhin 2007). It is defined by the presence of sharply demarcated atrophic lesions at the macula secondary to the loss of photoreceptors, RPE, and choriocapillaris, causing loss of visual function (Fleckenstein 2017). It is typically a bilateral condition. The atrophic lesions tend to arise in the perifoveal regions initially, preserving the fovea ('foveal sparing'), before these lesions expand and coalesce over time to affect the fovea as well (Fleckenstein 2017).

Geographic atrophy can be observed clinically by slit-lamp biomicroscopy and it can be documented by using multiple imaging modalities, with the most common being a combination of colour fundus photography (CFP), fundus autofluorescence (FAF) imaging and optical coherence tomography (OCT). On autofluorescence, features of early and intermediate AMD can be determined (Lois 2002) since areas of geographic atrophy demonstrate reduced autofluorescence signal (Holz 2001; Schmitz-Valckenberg 2004). Often there is a zone with increased autofluorescence signal surrounding the area affected by geographic atrophy. Holz and colleagues, and Schmitz-Valckenberg and colleagues have suggested that these zones are at higher risk for geographic atrophy expansion (Holz 2001; Schmitz-Valckenberg 2004).

The rate of progression of geographic atrophy is highly variable, ranging from 0.53 to 2.6 mm²/year (Fleckenstein 2017; Holz 2007; Klein 2008; Lindblad 2009; Schmitz-Valckenberg 2016; Sunness 2007), depending on the technology used to determine geographic atrophy and also on various patient-related prognostic factors, including larger baseline lesion size, presence of multifocal lesions,

specific autofluorescence patterns and parafoveal atrophic lesions (Fleckenstein 2017). The median time for parafoveal geographic atrophy to expand into the fovea is approximately 2.5 years according to one study (Lindblad 2009).

The condition of the fellow eye is also considered to be an important prognostic indicator for progression of geographic atrophy. Thus, people with unilateral geographic atrophy are at high risk of developing geographic atrophy in the fellow eye, with an estimated median time of seven years (Lindblad 2009). In addition, the rate of geographic atrophy progression is highest if the fellow eye has geographic atrophy, while it is lowest if the fellow eye has only early or intermediate AMD (Fleckenstein 2017).

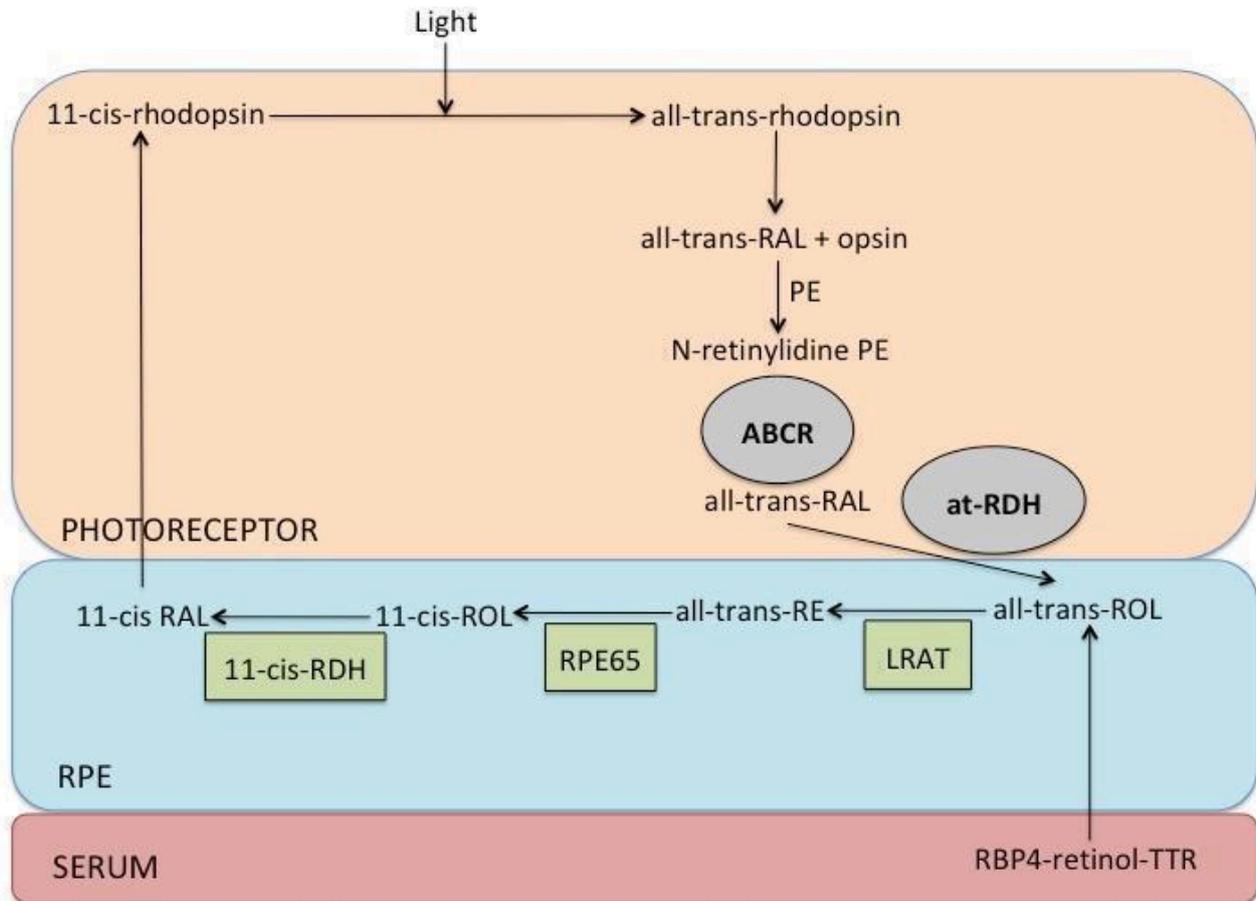
People with geographic atrophy experience scotomas (visual field defects), corresponding to the atrophic areas, whilst central vision is preserved to varying degrees if the fovea is spared (Sunness 1995). However, people will experience a drop in central visual acuity once the fovea is involved. In an observational study, 53% of geographic atrophy participants (initially not involving the fovea) suffered a 3-line loss of visual acuity by four years. Eyes with better visual acuity were observed to have the highest rate of visual acuity loss, with 27% dropping from 6/15 or better to 6/60 or worse in four years (Sunness 1999).

Description of the intervention

In the visual cycle, a series of enzymatic reactions takes place in the RPE and photoreceptor cells of the retina which, together with events occurring in the phototransduction cascade, enable generation of sight (Kiser 2014). Vitamin A (all-trans-retinol (all-trans-ROL)) is an essential part of this process, and its deficiency causes nyctalopia (night blindness), among other symptoms.

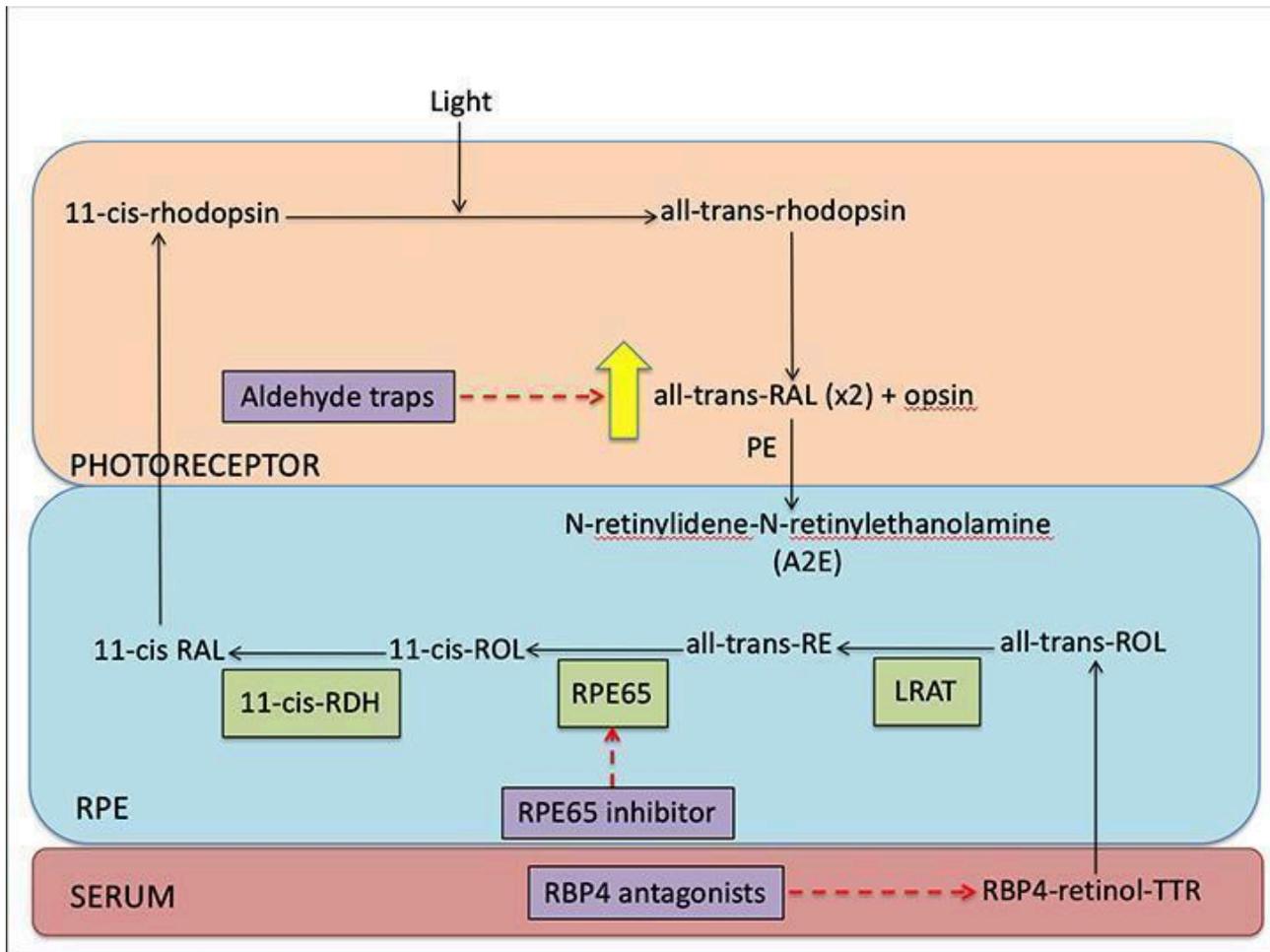
The main chromophore in the retina is 11-cis-retinal (11-cis-RAL) (Kiser 2014). It is normally bound to rhodopsin. When rhodopsin absorbs light, 11-cis-RAL undergoes isomerisation into all-trans-retinal (all-trans-RAL), and the rhodopsin becomes active, facilitating phototransduction (Kiser 2014). To enable continuous phototransduction, 11-cis-RAL is constantly recycled through the visual cycle (Figure 1). After all-trans-RAL is released from rhodopsin, it combines with phosphatidylethanolamine (PE), to form N-retinylidene PE. This is then transported to the cytosolic side of the disc membrane via the ATP-binding cassette transporter of the retina (ABCR), where all-trans-retinol dehydrogenase (at-RDH) resides. There, all-trans-RAL is reduced by the at-RDH into all-trans-retinol (all-trans-ROL), which will then enter the RPE and, through a series of enzymatic reactions, will be converted again into 11-cis-RAL, which will then return to the photoreceptors to be used again (Crouch 2009).

Figure 1. The visual cycle ABCR: ATP binding cassette of the retina; at-RDH: all-trans retinol dehydrogenase; RBP4-retinol-TTR: retinol binding protein-retinol- transthyretin complex; LRAT: lecithin-retinol acyltransferase; all-trans-RE: all-trans-retinyl ester; 11-cis-RDH: 11-cis-retinol dehydrogenase



Visual cycle modulators are pharmacologic agents that slow down the visual cycle. This can be achieved through various mechanisms (Figure 2).

Figure 2. N-retinylidene-N-retinylethanolamine (A2E) formation and mechanism of action of various visual cycle inhibitors (VCIs). Emixustat is an RPE65 inhibitor while fenretinide is an RBP4 antagonist.



- Inhibition of key visual cycle enzymes
- Retinol binding protein 4 (RBP4) antagonists
- Scavengers of free all-trans-RAL (aldehyde traps)

How the intervention might work

Several pathogenic mechanisms may be involved in the occurrence and progression of geographic atrophy, of which accumulation of lipofuscin (wear and tear pigment) in the RPE is probably one of those most widely accepted (Dorey 1989; Holz 2001; Schmitz-Valckenberg 2004). The major and best-characterised component of lipofuscin is N-retinylidene-N-retinylethanolamine (A2E) (Dugel 2015; Sparrow 2003). A2E is formed when two molecules of all-trans-RAL react with PE (Figure 2). It has been proposed that with ageing, RPE cell loss leads to reduced phagocytosis of metabolic waste products from photoreceptor disc membranes. The inefficiency of the remaining RPE cells to clear these waste products causes an accumulation of free all-trans-RAL and increased formation of A2E (Dorey 1989; Sparrow 2003). A2E damages RPE cells through generation of reactive oxygen species, causing dysfunction in the protein transportation within the cells, complement activation, up-regulation of vascular endothelial growth factor (VEGF), and introduction of premature cell death (Bavik 2015). In order to reduce A2E and lipofuscin formation,

Hanus and colleagues proposed slowing down the visual cycle by pharmacologic means to prevent or reduce progression of geographic atrophy (Hanus 2016).

One of the key visual cycle enzymes, RPE65 converts all-trans-RE to 11-cis-ROL, which is then reduced to 11-cis-RAL. In a study utilising ABCR knockout mice (known to accumulate excess lipofuscin in the RPE), Bavik and colleagues observed that treatment with an RPE65 inhibitor (emixustat) for three months caused a reduction of A2E formation by approximately 60% compared with controls (Bavik 2015). The effect was dose-dependent.

The supply of retinol is key to the visual cycle. In the body, serum retinol is normally bound to RBP4 to form the retinol-RBP4-transthyretin (TTR) complex to prevent rapid renal elimination. RBP4 needs to bind with retinol in order to activate binding with TTR (Petrukhin 2013). RBP4 antagonists (such as fenretinide and A1120) act by displacing retinol from RBP4 and thus disrupt the formation of retinol-RBP4-TTR complex and lead to the loss of retinol through the urine (Dobri 2013; Radu 2005). Intraperitoneal administration of fenretinide for 28 days and oral administration of A1120 for six weeks in ABCR knockout mice have shown a dose-dependent reduction of A2E levels (Dobri 2013; Radu 2005). This was correlated with reduced autofluorescence levels when the

fenretinide-administered mice were examined post-mortem (Radu 2005).

Another way proposed to reduce A2E production is by trapping free all-trans-RAL in the photoreceptors by utilising primary amine-containing drugs. These serve as a direct competitor of phosphatidylethanolamine (PE) to bind with free all-trans-RAL (Maeda 2011). In a study conducted with ABCR and at-RDH-deficient mice, 24 Food and Drug Administration (FDA) approved drugs containing primary amines picked from the Physicians' Desk Reference were tested and shown to protect against light-induced retinal damage as demonstrated on optical coherence tomography and post-mortem histology analysis (Maeda 2011).

Randomised controlled trials have evaluated visual cycle modulators, including emixustat and fenretinide, for the treatment of people with AMD and geographic atrophy. These medications are delivered orally and appear to be safe. Fenretinide has been used widely to treat or prevent different types of cancer and has been shown to be safe after many years of continuous treatment. The duration of treatment for visual cycle modulators is unknown at present but it is expected that life-long treatment may be needed in a progressive condition such as AMD.

Slowing down the rate of vitamin A dimerisation and therefore A2E production is another pharmacological approach which has strong pre-clinical evidence (Charbel Issa 2015; Ma 2011). Deuterated vitamin A, or ALK-001, is a synthetic vitamin A molecule made by incorporating deuterium (a stable and non-radioactive isotope) to the carbon-20 position of vitamin A (C20-D₃-vitamin A). We did not include ALK-001 in the current review as there are contradictory views about its mechanism of action. While some investigators have considered ALK-001 a visual cycle modulator (Hussain 2018b; Lu 2017), others have not (Charbel Issa 2015; Scholl 2019; Sears 2017).

Why it is important to do this review

AMD is the most common cause of blindness in high-income countries and the third most common in the world, with 8.7% of the world's population affected by this disease (WHO 2002; Wong 2014). The number of affected individuals is projected at 196 million in 2020 and 288 million in 2040 as a result of an increasingly ageing population (Wong 2014). Visual impairment secondary to AMD is associated with reduced quality of life (Lamoureux 2011), and a high economic burden, estimated to be 575 million US dollars in the USA in 2004 (Rein 2006).

With the introduction of anti-VEGF therapy, there are now well-established treatment regimens for neovascular AMD, which have been shown to stabilise, and in a small proportion to improve, vision in people affected by this disorder (Brown 2006; Rosenfeld 2006). However, the search for effective treatments for geographic atrophy continues.

As geographic atrophy is a slow and progressive condition, there is time for intervention before the retina is destroyed and certainly before the central fovea is affected, causing deterioration in central visual acuity. In addition, FAF imaging provides an accurate and validated method to monitor geographic atrophy progression, allowing clinicians and researchers to determine the efficacy of potential interventions. Similarly, spectral domain optical coherence tomography (SD-OCT) can provide important

information on early changes occurring in geographic atrophy due to AMD (Guymer 2019). Microperimetry can be used to assess retinal function. Thus, these technologies help researchers establish structural-functional correlations in areas with no overt atrophy and those with incipient and stabilised atrophy.

Given the projected increasing prevalence of AMD and its associated burden, it is of the utmost importance to develop therapies for the treatment and prevention of geographic atrophy. Researchers are investigating new therapies for atrophic AMD with variable results (Hanus 2016). Among these therapies are visual cycle modulators, which are the subject of this review.

OBJECTIVES

To assess the efficacy and safety of visual cycle modulators for the prevention and treatment of geographic atrophy secondary to AMD.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel group randomised controlled trials (RCTs) and quasi-randomised clinical studies. As visual cycle modulator use for the treatment and prevention of geographic atrophy is relatively new, we expected that randomised clinical trials using these therapies could be sparse. Thus, we planned to include quasi-randomised studies, as these could still provide useful information despite their limitations.

We included studies published as abstracts or conference presentations if sufficient details were presented to allow an appraisal of the methodology and the results. This could occur if a protocol for the study has been published previously.

Types of participants

People diagnosed with AMD (early, intermediate or advanced AMD), using validated methods/classifications (identified through either, or a combination of, clinical examination, fundus photography (CFP), FAF imaging, angiography or SD-OCT), with no age, gender or ethnicity restrictions. In people with advanced AMD, we included only those with the atrophic form of the disease (geographic atrophy); we did not include people with neovascular AMD.

Types of interventions

The main intervention was visual cycle modulators, which are also known as visual cycle inhibitors or by their mechanisms of action or by their drug name in the literature. The visual cycle modulators we were interested in included, but were not limited to, emixustat (ACU-4429) and fenretinide. We could not evaluate other drugs at earlier stages in development, but we noted these for assessment, if possible, in future updates of this review.

The comparator was placebo or no treatment (observation).

Types of outcome measures

Primary outcomes

- Mean change in best-corrected visual acuity (BCVA), from baseline to month 24.

Secondary outcomes

We determined the following outcomes at 24 months.

- Percentage of people losing 15 letters or more of BCVA
- Percentage of people losing 10 letters or more of BCVA
- Percentage of people losing 5 letters or more of BCVA
- Progression (growth of existing or development of new areas) of geographic atrophy (as measured using either, or a combination of CFP, FAF or fundus fluorescein angiography [FFA]). The mean geographic atrophy progression rate (mm²/year), measured using either FAF or CFP must have a difference of more than 0.02 mm² across groups to be considered a relevant difference beyond potential variability in the measures of geographic atrophy (Domalpally 2016).
- Progression to advanced AMD (geographic atrophy or neovascular AMD), in prevention studies including participants with early or intermediate AMD.
- Mean change in macular sensitivity, as measured with macular microperimetry, in prevention studies including participants with early or intermediate AMD.

If a study did not have a follow-up period of up to 24 months, last result reported at the end of the study was compared to baseline values for all the above parameters.

Adverse effects

We investigated ocular, systemic and serious adverse effects (e.g. all-cause death, serious systemic adverse events) and reactions, observed in treatment and comparator groups.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases for randomised controlled trials and controlled clinical trials:

- Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (2020, Issue 1) (searched 10 January 2020) (Appendix 1).
- MEDLINE Ovid (1946 to 10 January 2020) (Appendix 2).
- Embase Ovid (1980 to 10 January 2020) (Appendix 3).
- Web of Science (1970 to 11 January 2020) (Appendix 4).
- Scopus (1788 to 11 January 2020) (Appendix 5).
- Association for Research in Vision and Ophthalmology (ARVO) website (iovs.arvojournals.org/; searched 11 January 2020) (Appendix 6).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 11 January 2020) (Appendix 7).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictip; searched 11 January 2020) (Appendix 8).

The search covered 2005 to 11 January 2020 and there were no language restrictions.

Searching other resources

We checked reference lists of reviews and existing studies for relevant studies and used the Cited Reference Search function in Web of Science to identify articles that have cited studies identified for inclusion in the review.

Data collection and analysis

Selection of studies

Two review authors independently screened titles and abstracts retrieved from the searches to identify all citations that appeared likely to meet the inclusion criteria. In general, we did not document in this review citations considered not relevant at this stage, other than to note the number of these in a flow chart (Moher 2009). One review author retrieved the full manuscripts of relevant studies and assessed them for eligibility, and the second review author checked them. We documented the excluded studies after the full-text review stage.

We resolved any disagreements between the two review authors by discussion or by arbitration by a third review author when needed. We did not mask the names of the authors, institutions, or journals when reviewing studies.

Data extraction and management

Two review authors (JLY and NL) extracted data from the included studies using a standard data extraction form and entered the data into RevMan 5 (Review Manager 2014). We resolved any discrepancies with the data extracted by discussion. We extracted data related to study characteristics (Appendix 9), study methods and outcomes. We resolved any discrepancies or disagreements by discussion or by arbitration from a third review author if needed. We contacted study authors for missing or unclear data.

Assessment of risk of bias in included studies

We used the Cochrane 'Risk of bias' checklist. Two review authors (JLY and NL) assessed the included studies for risk of bias and we resolved any discrepancies by discussion. We assessed the following domains for each included study as described in Chapter 8 of the *Cochrane Handbook for Systematic Review of Interventions* (Higgins 2019).

- Selection bias: sequence generation and allocation concealment
- Performance bias: masking of participants and personnel
- Detection bias: masking of outcome assessment
- Attrition bias: incomplete outcome data
- Reporting bias: selective outcome reporting. If the protocol or clinical trials registry record for the included study was available, we evaluated the study for evidence of systematic differences between reported and unreported findings.

We assessed each 'Risk of bias' domain as low, high or unclear, and provide descriptions as to our reasoning for such assessments. We resolved disagreements by discussion.

Measures of treatment effect

We calculated the mean difference (MD) with 95% confidence intervals (CIs) for outcome measures reported as continuous data (mean change in BCVA, mean change in area of geographic

atrophy). We calculated the risk ratio (RR) with 95% confidence intervals for outcome measures reported as dichotomous data (proportion with loss of BCVA, progression to advanced AMD, adverse events).

Unit of analysis issues

All the included studies randomised a single eye per participant to a single intervention. In cases where both eyes of participants were included and analysed with the eye as the unit of analysis, we would have attempted to analyse the data adjusting for clustering or paired-eye design as appropriate, as described in the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2017). If an RCT had multiple arms evaluating different treatment doses, when no dose-response was observed, we combined data from all dose groups for analysis as described in Chapter 7 (section 7.7.3.8) of the Cochrane Handbook for Systematic Review of Interventions (Higgins 2019). We then calculated and presented the treatment effect (mean difference (MD) for continuous data or risk ratio (RR) for dichotomous data) and its respective 95% CI.

Dealing with missing data

We attempted to contact the corresponding authors of all three studies to obtain missing data but only two replied (Mata 2013; SEATTLE Study). The corresponding author from Mata 2013 was not able to provide us with more information. The corresponding author from SEATTLE Study answered all our queries. We did not impute data for the purposes of this review.

Assessment of heterogeneity

We assessed included studies for clinical, methodological and statistical heterogeneity. Meta-analysis was not possible as the outcomes reported in the two emixustat trials identified were heterogeneous, and only one fenretinide trial was included.

Assessment of reporting biases

We could not assess publication bias with the funnel plot and Egger's regression intercept as there were only three studies included in this review and meta-analysis was not possible. We assessed for potential selective outcome reporting by study as part of the 'Risk of bias' assessment (Egger 1997; Sterne 2017).

Data synthesis

We did not proceed with our plan to conduct meta-analysis because the reporting of visual and anatomical outcomes differed among identified trials, precluding pooling them in meta-analysis.

Subgroup analysis and investigation of heterogeneity

We planned to analyse studies undertaken to evaluate prevention of advanced AMD (geographic atrophy or neovascular AMD) in participants with early or intermediate forms of the disease, separately from those undertaken in studies evaluating treatment of people with already established geographic atrophy. However, we identified no trials.

Sensitivity analysis

We planned to perform the following sensitivity analyses on the primary outcome.

- Excluding studies defined as 'high risk' of bias in one or more domains based on the Cochrane 'Risk of bias' checklist
- Comparing fixed-effect and random-effects models (if there are three or more studies)

However, this was not possible as the two emixustat trials identified were heterogeneous, we included only one fenretinide trial in this review.

Summary of findings and assessment of the certainty of the evidence

We prepared a 'Summary of findings' table to present estimated relative and absolute risks (GRADEpro GDT). Two review authors (JLY and NL) independently graded the overall quality of the evidence for each outcome using the GRADE classification (Guyatt 2008). We included the following outcomes in the 'Summary of findings' table at 24 months or at the end of the study period if a trial had a shorter follow-up period (Schünemann 2017).

- Mean change in BCVA
- Proportion of participants losing 15 letters or more of BCVA
- Proportion of participants losing 10 letters or more of BCVA
- Progression of geographic atrophy
- Progression to advanced AMD (geographic atrophy or neovascular AMD)
- Mean change in macular sensitivity
- Adverse events: all-cause mortality, all serious systemic adverse events

We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias), grading the evidence for each outcome as high, moderate, low or very low. We justified all decisions to down- or upgrade the quality of studies using footnotes and comments to aid readers' understanding of the review where appropriate.

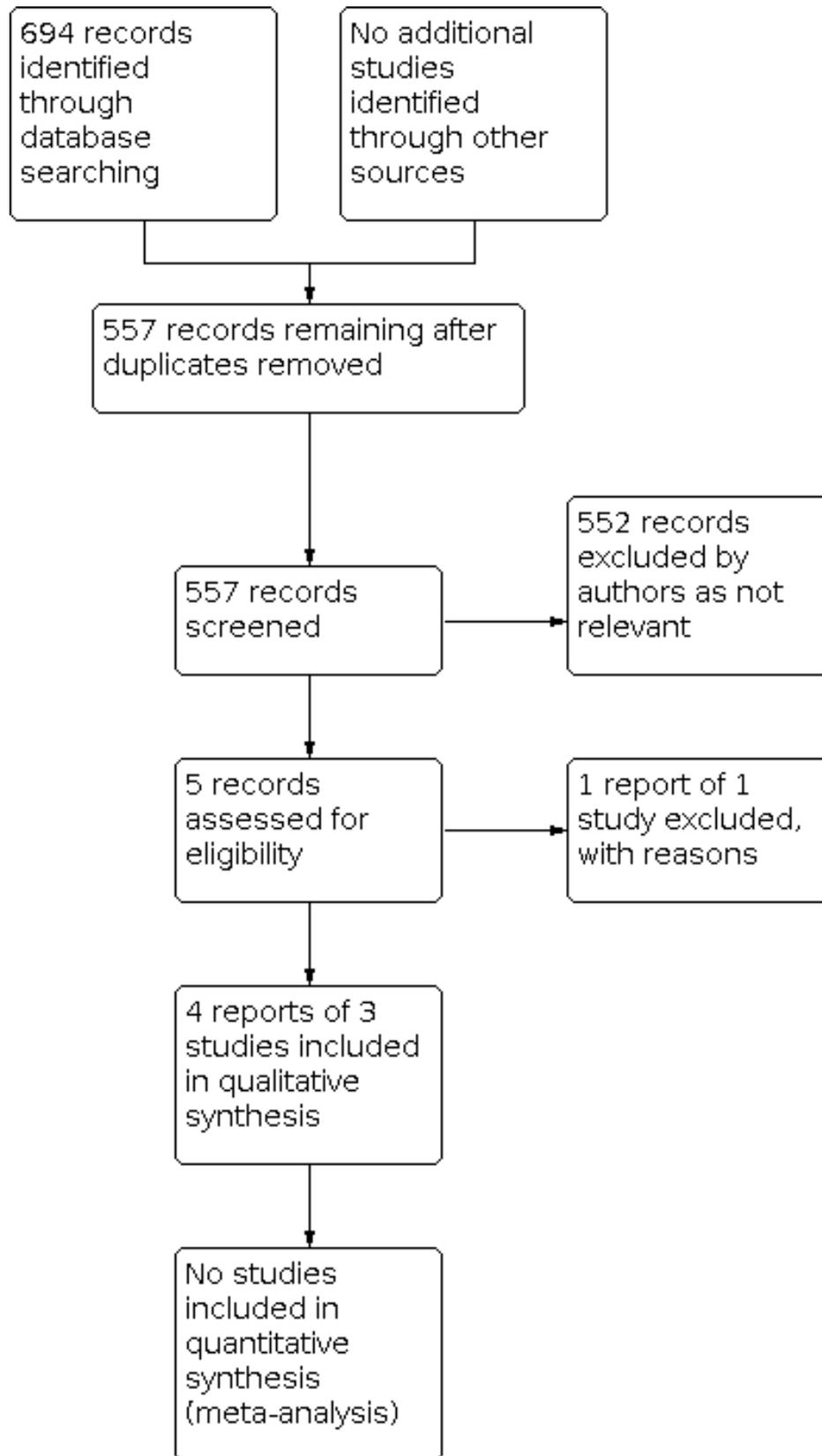
RESULTS

Description of studies

Results of the search

The original search resulted in 694 records. After 137 duplicates were removed, we screened the remaining 557 records. We excluded 552 records after assessing the titles and abstracts. We screened the full-text reports of the remaining five records (Figure 3). Four full-text reports of three trials (SEATTLE Study had two reports) were eligible and, thus, included in this systematic review. The excluded article was an editorial by Boman (Boman 2010).

Figure 3. Study flow diagram.



Included studies

We included three studies in this review ([Dugel 2015](#); [Mata 2013](#); [SEATTLE Study](#)). See the [Characteristics of included studies](#) table for further information.

Study design

All three studies were multicentre, double-masked, placebo-controlled randomised clinical trials (RCTs). Of the three trials included, two were phase 2a trials ([Dugel 2015](#) ; [Mata 2013](#)) and one was a phase 2b/3 trial ([SEATTLE Study](#)). [Dugel 2015](#) was a dose-ranging study investigating the safety and pharmacodynamics of the RPE65 inhibitor, emixustat, over a 90-day period. This phase 2a study was followed by the phase 2b/3 by [SEATTLE Study](#), which investigated the efficacy and safety of emixustat for the same indication over a 24-month period. It was not stated in [SEATTLE Study](#) whether the participants in the phase 2a ([Dugel 2015](#)) study were invited to participate and indeed took part in the phase 2b/3 trial. [Mata 2013](#) investigated the safety and efficacy of the RBP4 inhibitor, fenretinide, over 24 months.

Participants

The three trials randomised 821 participants in total. The studies were conducted in the USA ([Dugel 2015](#) ; [SEATTLE Study](#)) and Germany ([SEATTLE Study](#)). [Mata 2013](#) did not state where the participants were recruited. The majority of participants were white (n = 801, 97.6%). The median age range of participants was 75.5 to 82 years in [Dugel 2015](#) and [Mata 2013](#), and the mean age range reported in [SEATTLE Study](#) was 77.1 to 78.2 years.

All participants had established geographic atrophy due to AMD. The atrophic lesion sizes were measured using a combination of CFP, FAF imaging and FFA ([Dugel 2015](#); [Mata 2013](#)) or FAF alone ([SEATTLE Study](#)). The mean baseline lesion size of participants in [SEATTLE Study](#) was between 6.7 to 7.0 mm² as measured by FAF. The median baseline lesion size for [Dugel 2015](#) was between 7.38 to 11.77 mm² as measured by FFA. The median baseline lesion size for [Mata 2013](#) measured by CFP was between 8.1 to 9.06 mm², while it was between 8.33 to 9.02 mm² when measured with FAF.

The median baseline BCVA for all three studies ranged from 52.5 to 70 letters as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart.

Interventions

All three trials compared treatment with visual cycle modulators to placebo.

The RPE65 inhibitor, emixustat, was investigated in two trials ([Dugel 2015](#); [SEATTLE Study](#)).

[Mata 2013](#) investigated the RBP4 inhibitor, fenretinide.

Primary Outcome

The primary outcome for our review was mean change in BCVA from baseline to month 24 or at the end of study if a trial did not have a follow-up period of 24 months.

Of the three studies, only [Mata 2013](#) and [SEATTLE Study](#) reported this outcome at month 24. However, [Mata 2013](#) did not provide

numerical data on mean change in BCVA (although measured in the study); data were presented only in the manuscript in a graph format. Although we contacted the corresponding author for this information, it was not provided.

[Dugel 2015](#) did not report on this outcome even though BCVA was measured during the follow-up period. We attempted to contact the corresponding author to obtain this information but received no response.

Secondary Outcomes

The secondary outcome measures that we stated in our protocol were:

- Percentage of participants losing 15 letters or more in BCVA;
- Percentage of participants losing 10 letters or more in BCVA;
- Percentage of participants losing 5 letters or more in BCVA;
- Progression of geographic atrophy (growth of existing or development of new areas) as measured using either, or a combination of CFP, FAF or FFA;
- Progression to advanced AMD (geographic atrophy or neovascular AMD) in prevention studies including participants with early or intermediate AMD;
- Mean change in macular sensitivity as measured with macular microperimetry, in prevention studies including participants with early or intermediate AMD.

All secondary outcomes were determined at 24 months or end of the trial if it had a follow-up period of less than 24 months.

All three RCTs reported progression of geographic atrophy in both intervention and control arms either measured by CFP, FAF, FFA or any combination of these three modalities. [Dugel 2015](#) reported mean lesion size change (mm²) from baseline to day 90 (end of study period) measured with CFP, FAF and FFA. [Mata 2013](#) reported median annual lesion growth rate (mm²/year) measured with CFP, while [SEATTLE Study](#) reported mean annual lesion growth rate (mm²/year) as measured by FAF.

[SEATTLE Study](#) reported percentage of participants losing ≥ 15 letters of BCVA but not the percentages of people losing ≥ 5 or ≥ 10 letters of BCVA. The other two studies did not report any of these visual outcomes ([Dugel 2015](#) ; [Mata 2013](#)).

None of the studies evaluated mean change in macular sensitivity, as measured with macular microperimetry. As none of the three studies recruited participants with early or intermediate AMD, data pertaining to progression to advanced AMD (geographic atrophy or neovascular AMD) were not available.

Excluded studies

We excluded one study ([Boman 2010](#)), details of which are provided in the [Characteristics of excluded studies](#) table. This study was an editorial and was not excluded based on outcome measures.

Risk of bias in included studies

See [Figure 4](#) for the “Risk of bias” graph and [Figure 5](#) for the “Risk of bias” summary.

Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

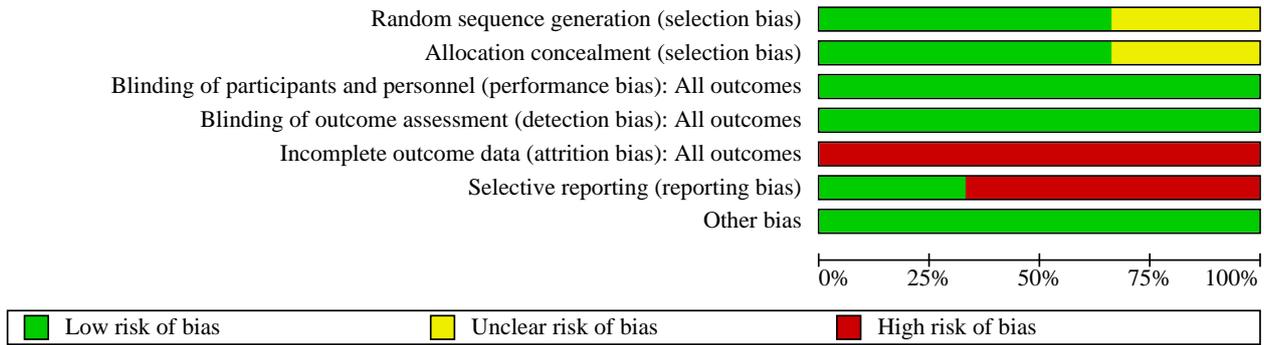
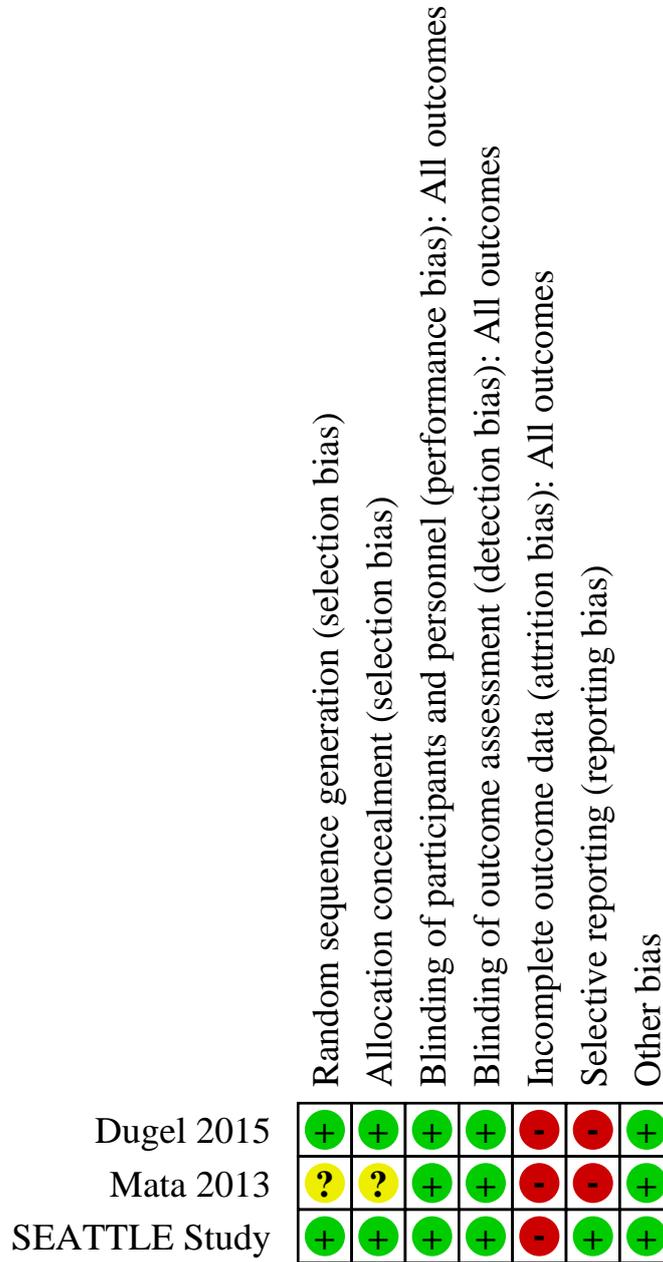


Figure 5. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Two studies reported an adequate method of randomisation: [Dugel 2015](#) used a computer-generated randomisation code and [SEATTLE Study](#) used an interactive web-response system. Although participants in [Mata 2013](#) were randomised, the method used to achieve randomisation was not reported. [Dugel 2015](#) had adequate allocation concealment where the randomisation code

was kept under lock and key. In [SEATTLE Study](#), although details on allocation concealment were not mentioned in the published manuscript, the authors confirmed upon enquiry that allocation concealment was achieved by having all the study medication tablets (emixustat and placebo) appearing identical and supplied in blister-card packaging with identical dosages. [Mata 2013](#) did not report the method used to conceal allocation.

Blinding

All the studies were conducted as 'double-masked' RCTs, whereby participants and outcome assessors were masked to treatment allocation and therefore had low risk of performance and detection biases.

Incomplete outcome data

All three studies had high risk of attrition bias.

In [Dugel 2015](#), only 59.7% of the total assigned participants completed the 90-day study period. Forty-three per cent from the emixustat arm and 33% from the placebo arm did not complete the study. Two treatment arms (7 mg emixustat and 10 mg emixustat) and their corresponding placebo arms were discontinued early due to concerns regarding frequency and severity of adverse events. Hence, median exposure time to emixustat in these two treatment arms (25 days) was less than other treatment arms (90 days).

In [Mata 2013](#), the two treatment arms had a higher number of dropouts compared to placebo. In the fenretinide 100 mg and fenretinide 300 mg arms, 35% and 31% of participants, respectively, withdrew, compared to 17% of participants assigned to placebo. Trial design stated that analysis of annual lesion growth rate was performed on an intention-to-treat analysis for all randomised participants who were dosed at least once and had at least two follow-up visits after six months. However, annual lesion growth rate was only evaluated in participants who completed at least 18 months of treatment.

In [SEATTLE Study](#), 57.3% of participants from the combined emixustat arm (58.6% of the 2.5 mg arm, 60.4% of the 5 mg arm and 51.5% of the 10 mg arm) and 81.2% from the placebo arm completed the study.

Selective reporting

Two studies ([Dugel 2015](#); [Mata 2013](#)) were judged to have high risk of reporting bias. In [Dugel 2015](#), some of the outcome data were reported as summary statements instead of point estimates with measurement of variability. Pharmacokinetics was listed as one of the outcome measures on the trial registry but this was not reported in the published article. Additionally, the study only reported ocular adverse events that had two or more participants affected in the total emixustat arm.

In [Mata 2013](#), the annual lesion growth rate measured by FAF was not reported. Instead, it was only stated as having "excellent agreement" with the data analysed from CFP. The systemic adverse events reported in the published manuscript were unclear. The authors only provided details for the "skin and subcutaneous" system, which were rash and pruritus but no further information was given for the other systems. [SEATTLE Study](#) reported all primary and secondary outcomes.

Other potential sources of bias

There were no other potential sources of bias.

Effects of interventions

See: [Summary of findings 1](#) Emixustat compared to placebo for people with geographic atrophy due to AMD; [Summary of findings 2](#) Fenretinide compared to placebo for people with geographic atrophy due to AMD

Emixustat vs placebo

Two studies investigated this comparison ([Dugel 2015](#); [SEATTLE Study](#)). See [Summary of findings 1](#).

[Dugel 2015](#) randomised 54 participants to emixustat and 18 participants to placebo with a study period of 90 days. Each emixustat group (2 mg once in the morning; 5 mg once in the morning; 7 mg once in the morning; 10 mg once in the morning; 5 mg once in the evening) had a corresponding control group. [SEATTLE Study](#) randomised 370 participants to emixustat and 133 participants to placebo with a study period of 24 months.

Meta-analysis was not possible as the outcomes reported were heterogeneous.

Fenretinide vs placebo

[Mata 2013](#) was the only study that investigated this comparison (see [Summary of findings 2](#)). The study randomised 164 participants to the fenretinide cohorts and 82 participants to placebo with a study period of 24 months.

There was inconsistent reporting of results and adverse events in this study. After randomisation, 82, 80 and 84 participants were assigned to the placebo, fenretinide 100 mg and fenretinide 300 mg arms, respectively. However, tables presented in the results section only had 83 participants in the 300 mg arm with no explanation of the one missing participant. Tables representing withdrawal rates in the trial and ocular adverse events not leading to study withdrawal were reported in terms of number of participants or percentage of participants. Tables representing total incidence of adverse events and ocular adverse events leading to study withdrawal were reported in terms of number of reported events.

Meta-analysis was not possible as this was the only study on fenretinide included in this review. The treatment effect (MD for continuous data or RR for dichotomous data) and its respective 95% CI are presented.

1) Mean change in BCVA from baseline to month 24

Emixustat vs placebo ([Analysis 1.1](#))

Only [SEATTLE Study](#) reported on the primary outcome of mean change in BCVA from baseline to month 24 (or end of study). [Dugel 2015](#) did not report on any visual outcomes that were listed in our protocol. Participants taking emixustat had a mean loss of 5.8 letters (SE 1.8) compared to the placebo cohort, who lost 7.7 letters (SE 1.2) (MD 1.9 letters, 95% CI -2.34 to 6.14, 320 participants). We judged this to be low-certainty evidence; we downgraded one level for risk of bias and one level for imprecision due to a large range of confidence interval, ranging from -2 to 6 letters. A difference of less than 10 ETDRS letters is not regarded as clinically relevant ([Moseley 2011](#)) and a difference of 6.5 ETDRS letters may be due to test-retest variability.

Fenretinide vs placebo

[Mata 2013](#) reported this outcome in a graphical format instead of numerical data. The data points on the graph were not clear enough for us to extract to perform data analysis. Only a statement was provided in the text: "... 2-year loss of 10 to 11 letters in all treatment groups". A greater visual acuity loss was observed in the 300 mg arm at 12-18 months though this was considered to be statistically

insignificant. This was despite the fact that more participants in the 300 mg arm (81%) had lesions involving or encroaching the fovea at baseline compared to placebo (70%). However, we are unsure if only participants who have completed at least 18 months of the study are included in this analysis.

We judged this to be low-certainty evidence; we downgraded one level each for risks of attrition and reporting biases.

2) Percentage of participants losing ≥ 15 letters

Emixustat vs placebo (Analysis 1.2)

Only [SEATTLE Study](#) reported this outcome. The corresponding author clarified that this outcome was based on each participant's most recent visit (after baseline), whenever that occurred during the study period (this information is not contained in the published manuscript). A final BCVA score was obtained from participants at the 30-day off study drug visit (month 25) if they had completed the planned 24-month study visit. For participants who withdrew prior to study completion (month 24), investigators attempted to obtain a final BCVA score 30 days after the termination date. Among those who withdrew early, the investigators were not able to obtain a follow-up BCVA score for five participants (all treated with emixustat).

Of participants taking emixustat, 16.4% (60/365) lost ≥ 15 letters at their last follow-up visit compared to 18% in the placebo group (24/133) (RR 0.91, 95% CI 0.59 to 1.40, 498 participants). We judged this to be low-certainty evidence after downgrading one level each for risk of bias and imprecision.

Fenretinide vs placebo

This was not reported in [Mata 2013](#).

3) Percentage of participants losing ≥ 10 letters

Emixustat vs placebo

This was not conducted in [Dugel 2015](#) and [SEATTLE Study](#).

Fenretinide vs placebo

This was not conducted in [Mata 2013](#).

4) Progression of geographic atrophy (mm^2/year)

Emixustat vs placebo (Analysis 1.3)

[SEATTLE Study](#) reported this outcome based on measurements using FAF for each treatment arm (2.5 mg, 5 mg, 10 mg and placebo). The mean annual growth rate of the pooled emixustat arm was $1.78 \text{ mm}^2/\text{year}$ (SE 0.14) while it was $1.69 \text{ mm}^2/\text{year}$ (SE 0.11) in the placebo arm (MD 0.09 mm^2/year , 95% CI -0.26 to 0.44, 503 participants). We judged this to be low-certainty evidence; we downgraded one level for risk of bias and one level for imprecision due to a large range of confidence interval, ranging from -0.26 to $0.44 \text{ mm}^2/\text{year}$.

Fenretinide vs placebo (Analysis 2.1)

[Mata 2013](#) reported this outcome based on measurements using CFP for each treatment arm (100 mg, 300 mg and placebo). The median growth rate in the fenretinide 100 mg arm was $2.14 \text{ mm}^2/\text{year}$ (SD 1.66), fenretinide 300 mg arm was $1.95 \text{ mm}^2/\text{year}$ (SD 1.22)

and the placebo cohort was $2.03 \text{ mm}^2/\text{year}$ (SD 1.24). Confidence intervals were not provided for these comparisons. We judged this to be low-certainty evidence; we downgraded one level for risk of bias and a further level for reporting bias as the distribution of participants with previous CNV history in the study eye was not reported.

A subgroup analysis was performed for participants in both the fenretinide 100 mg and 300 mg arms who achieved serum RBP levels of $\leq 2 \text{ mg/dL}$, equivalent to a retinol concentration of $\leq 1 \text{ }\mu\text{mol}$. Twenty-one participants from the 300 mg cohort who met this criterion had a median growth rate of $1.7 \text{ mm}^2/\text{year}$ (SD 0.77) compared to $2.03 \text{ mm}^2/\text{year}$ (SD 1.24) measured in the placebo arm. The P value was 0.185 but a confidence interval was not provided. A similar trend was observed in the 100 mg cohort but only 10 participants achieved this level of serum RBP reduction, precluding any definitive conclusion.

We did not report this outcome in [Analysis 2.1](#) as this was not pre-specified in the methodology section or in the trial registry record.

5) Mean change in macular sensitivity

Emixustat vs placebo

This was not conducted in [Dugel 2015](#) and [SEATTLE Study](#).

Fenretinide vs placebo

This was not conducted in [Mata 2013](#).

6) Adverse events

Emixustat vs placebo

[Table 1](#) summarises the reported adverse events related to emixustat in both studies ([Dugel 2015](#); [SEATTLE Study](#)). The most commonly reported adverse events were ocular in nature, with delayed dark adaptation and chromatopsia being the most common. These events were also the most commonly reported causes of study drug discontinuation in both studies. The ocular adverse events appeared to be dose-dependent and resolved after emixustat cessation.

In [Dugel 2015](#), time of recovery of rod b-wave amplitude after photobleaching was used as a marker for emixustat pharmacological activity. The trial reported that suppression of rod b-wave recovery rate was higher with increasing emixustat dose. The rod b-wave recovery rate subsequently returned to baseline levels in all emixustat groups 7 to 14 days after drug cessation.

[SEATTLE Study](#) reported that decreases of low luminance BCVA (LL-BCVA) letter score (measured by placing a 2.0 log unit neutral density filter over the best correction lens, if required) of ≥ 15 letters were more common in emixustat-treated participants than in the placebo group. A dose-dependent response was observed. The incidence decreased in the emixustat-treated participants to a level which was similar to the placebo group once treatment had ended.

In both studies, the placebo arms were observed to have higher incidence of systemic adverse events. Most events were considered by the investigators to be unrelated to emixustat. In [Dugel 2015](#), three emixustat-treated participants experienced serious adverse events which subsequently resolved (see [Table 1](#)). The incidences of serious adverse events in [SEATTLE Study](#) were similar between

the emixustat (20.8%) and the placebo (22.6%) arms. There were no participant deaths during the period of the study in [Dugel 2015](#) while six participants died in [SEATTLE Study](#). All six participants had received emixustat but the investigators determined that the deaths were not related to the drug.

We judged this to be moderate-certainty evidence; we downgraded one level for risk of attrition bias in both studies and reporting bias in [Dugel 2015](#).

Fenretinide vs placebo

[Table 2](#) summarises the reported adverse events related to fenretinide. The most commonly reported adverse events were ocular in nature, with delayed dark adaptation and visual disturbance (described as transient pattern of colour or darkened areas within the visual field upon waking or during an immediate exposure to bright light) being the most common in fenretinide-treated participants. These events were dose-dependent and visual disturbance resolved shortly after drug cessation. Effect of drug cessation on delayed dark adaptation was not reported. Reduction in visual acuity was very common among both combined fenretinide and placebo arms. This observation may be confounded by the fact that more participants in the 300 mg arm (81%) had lesions involving or encroaching the fovea at baseline compared to placebo (70%).

The only systemic adverse events considered by the authors to be study drug-related were “skin and subcutaneous” disorders (rash and pruritus). Five events were reported in the combined fenretinide cohort compared to no events in the placebo cohort. No deaths occurred in either arm during the trial.

We judged this to be low-certainty evidence; we downgraded one level for risk of bias and one level for possible confounding effect as described above.

7) Other outcomes reported in the included studies that were not specified in our protocol

The following outcomes were not specified in our protocol but were reported in the included trials. Below is a summary of the results for each outcome:

a) Mean change in geographic atrophy lesion size (mm²)

Emixustat vs placebo

[Dugel 2015](#) reported the mean change in geographic atrophy lesion size at day 90 for each treatment arm (2 mg once in the morning, 5 mg once in the morning, 5 mg once in the evening and placebo) as measured by FAF ([Analysis 1.4](#)), FFA ([Analysis 1.5](#)) and CFP ([Analysis 1.6](#)).

The mean change in lesion size in the pooled emixustat arm seemed to be less than that in the placebo arm when measured on all three modalities. When measured with FAF, the mean change in the emixustat arm was -0.1 mm² (SE 1.1) compared to 0.2 mm² (SE 0.4) in the placebo arm (MD -0.3 mm², 95% CI -2.59 to 1.99, 31 participants). The mean change was 0.3 mm² (SE 0.4) in the emixustat arm and 0.4 mm² (SE 0.5) in the placebo arm (MD -0.1 mm², 95% CI -1.36 to 1.16, 43 participants) when measured with FFA. When measured with CFP, the mean change in the emixustat

arm was 0.2 mm² (SE 0.5) while it was 0.4 mm² (SE 0.7) in the placebo arm (MD -0.2 mm², 95% CI -1.89 to 1.49, 38 participants).

We judged this to be low-certainty evidence; we downgraded one level for risk of attrition bias and one level for imprecision.

b) Incidence of CNV onset

Emixustat vs placebo ([Analysis 1.7](#))

This outcome was reported in [SEATTLE Study](#) for the study eye only. CNV onset in the study eye was evaluated throughout the study period post-baseline visit. Of emixustat-treated participants, 3.55% (13/366) developed CNV in the study eye compared to 5.26% (7/133) in the placebo arm (RR 0.67, 95% CI 0.28 to 1.66, 499 participants). There appeared to be a dose-dependent relationship but the numbers are too small for us to draw any conclusion. We judged this to be low-certainty evidence after downgrading one level each for risk of bias and imprecision.

Among the 20 participants who developed CNV in the study eye, 60% of them had prior or current CNV in the non-study eye. It was reported that the percentage of participants who had prior or current CNV in the non-study eye at baseline was comparable between the emixustat 2.5 mg, 5 mg, 10 mg arms and the placebo arm.

Fenretinide vs placebo ([Analysis 2.2](#))

[Mata 2013](#) reported this outcome for either the study or fellow eye. Of fenretinide-treated participants, 9.2% (15/164) developed CNV compared to 18.3% (15/82) in the placebo arm (RR 0.5, 95% CI 0.26 to 0.98, 246 participants). We judged this to be low-certainty evidence; we downgraded one level each for risks of attrition and reporting biases. The authors reported that more than 90% of CNV events occurred in the study eye in each arm (100 mg, 300 mg and placebo); no exact figure or breakdown was provided.

DISCUSSION

Summary of main results

The trials identified in this review investigated two types of visual cycle modulators, emixustat ([Dugel 2015](#); [SEATTLE Study](#)) and fenretinide ([Mata 2013](#)). Both [Mata 2013](#) and [SEATTLE Study](#) had a study period of 24 months while [Dugel 2015](#), which was a preliminary study, had a duration of only 90 days. We were unable to perform meta-analyses for either emixustat or fenretinide due to the heterogeneity of emixustat trials and insufficient number of trials investigating fenretinide. Therefore, we have reported the outcomes in a narrative format.

Among studies on emixustat, the doses used in [Dugel 2015](#) were 2 mg once in the morning, 5 mg once in the morning, 5 mg once in the evening daily for 90 days. Arms with 7 mg once in the morning and 10 mg once in the morning were terminated early. Doses used by [SEATTLE Study](#) were 2 mg, 5 mg and 10 mg daily for 24 months. It was observed that there was little difference between the emixustat and placebo arms in terms of the visual outcomes reported (mean change in BCVA from baseline to month 24 and incidence of participants losing ≥15 letters). These results are presented in [Analysis 1.1](#) and [Analysis 1.2](#).

The progression rate of geographic atrophy (mm^2/year) measured on FAF in emixustat-treated participants was not significantly different from that in the placebo arm (MD 0.09 mm^2/year , 95% CI -0.26 to 0.44). The other additional anatomical outcomes reported in this review (mean change in geographic atrophy lesion size from baseline at day 90 as measured by FAF, FFA and CFP) may not be informative as geographic atrophy is recognised to be a slowly progressive condition. The results of these outcomes are presented in [Analysis 1.4](#), [Analysis 1.5](#) and [Analysis 1.6](#).

Fenretinide-treated participants in [Mata 2013](#) were assigned to 100 mg or 300 mg doses taken every evening for 24 months. Mean change in BCVA from baseline was reported in a graphical format, and therefore no accurate figures are available for each arm. When compared to placebo, the fenretinide 100 mg arm had a slightly higher median annual lesion growth rate and the 300 mg arm had a slightly lower rate but neither were statistically significant. The progression was slightly slower in the subgroup with greater retinol binding protein (RBP) response but again not significantly so. This is presented in [Analysis 2.1](#). The authors did not provide confidence intervals for either comparison with placebo.

Data were suggestive of a reduction in the incidence of CNV in participants treated with emixustat or fenretinide when compared to placebo. [SEATTLE Study](#) reported a reduced incidence of CNV development in emixustat-treated participants compared to placebo (RR 0.67, 95% CI 0.28 to 1.66); confidence intervals, however, were wide. A dose-dependent pattern was apparent in the emixustat-treated participants, with reducing incidence at higher doses (2.5 mg: 5.3%; 5 mg: 3.8%; 10 mg: 1%). Among the 20 participants who developed CNV in the study eye, 60% of them had previous history of CNV in their non-study eye and were therefore 'high risk' patients. In [Mata 2013](#), those treated with fenretinide were less likely to develop CNV in either the study or fellow eye compared to placebo (RR 0.5, 95% CI 0.26 to 0.98).

The adverse events reported for both interventions were mainly ocular in nature and were related to the mechanism of action of these visual cycle modulators. Chromatopsia and delayed dark adaptation were the most common treatment-associated adverse events in all three studies. The definition of 'visual disturbance', which was one of the reported adverse events in [Mata 2013](#), seems to describe chromatopsia. A dose-dependent pattern was observed for these events and resolved after drug cessation. Other reported ocular adverse events are in [Table 1](#) and [Table 2](#). There were no specific systemic adverse events associated with emixustat, while pruritus and rash were known to be associated with fenretinide based on previous studies ([Carmerini 2001](#); [Costa 1989](#); [De Palo 1995](#)).

Overall completeness and applicability of evidence

The population studied in all three trials was similar. Participants were adults between 53 and 95 years old, predominantly white and had a clinical diagnosis of geographic atrophy due to AMD, which was confirmed by masked central image reading centres.

All three included studies had high dropout rates of participants (43% in [Dugel 2015](#); 42.7% in [SEATTLE Study](#); 33.1% in [Mata 2013](#)) due to ocular adverse effects related to the treatment. The most frequently reported adverse events were delayed dark adaptation and chromatopsia, both of which were associated with the mechanisms of action of emixustat and fenretinide.

These adverse events were dose-dependent and resolved after drug cessation. Both drugs were generally not well tolerated by participants, which could have implications on compliance if used in future studies or in a real-world setting.

The visual and anatomical outcomes in the treatment arms (emixustat or fenretinide) of all trials included were similar to placebo. Participants on 300 mg doses of fenretinide did seem to have slower atrophic lesion growth rate especially if serum RBP levels were ≤ 2 mg/dL, but the difference did not achieve statistical significance. The results from these trials indicate that initiating treatment with visual cycle modulators at such an advanced stage of geographic atrophy has minimal impact on slowing retinal degeneration or preserving central visual function. There might be more therapeutic scope for these therapies in patients with intermediate AMD at high risk of progression but no such studies have been undertaken yet. High rates of dropout from clinical trials and the potentially poor compliance with these treatments should be taken into consideration if visual cycle modulators continue to be pursued for the treatment of AMD or other degenerative retinal diseases.

An interesting observation was the potentially lower incidence of CNV in the group of participants treated with either emixustat or fenretinide. Neovascular AMD, although less prevalent than geographic atrophy, causes more profound and sudden visual loss. Despite the success of anti-VEGF treatment, this therapy represents a significant treatment burden for both patients and healthcare systems due to an increasingly ageing population and the high cost of treatment ([Gale 2019](#); [Spooner 2018](#)). Furthermore, anti-VEGFs have potential significant side effects including endophthalmitis. Therefore, this particular finding might be worth exploring further due to the potential for visual cycle modulators to reduce the risk of CNV formation. Other more tolerable visual cycle modulators could be considered, given the frequent adverse effects associated with emixustat and fenretinide.

Quality of the evidence

Overall, only [SEATTLE Study](#) was well conducted, adequately powered and appropriately reported, with clear primary and secondary outcomes. We judged this study to have high risk of bias in only one domain (attrition bias) while other domains were of low risk of bias.

There were issues with the quality of reporting in both [Dugel 2015](#) and [Mata 2013](#). The baseline characteristics of participants in [Dugel 2015](#) were not balanced between treatment and placebo arms. Outcome data were either not fully reported (adverse events) or not reported at all (pharmacokinetics) by the authors. We judged this study to have high risk of bias in two domains (attrition bias and reporting bias).

In [Mata 2013](#), investigators reported that baseline ocular characteristics were similar across all groups. However, the fenretinide 300 mg arm had a higher percentage of participants with geographic atrophy involving or encroaching on the fovea (81%), compared to the fenretinide 100 mg (72%) and the placebo (70%) arms. However, investigators did not state whether these differences were statistically significant. Data on median annual lesion growth rate measured by FAF were not reported clearly in the manuscript, although this data contributed to the primary evaluation of efficacy of fenretinide. There was also inconsistent

reporting of the associated adverse events as elaborated in the [Effects of interventions](#) section (fenretinide vs placebo). We judged this study to have high risk of bias in two domains (attrition bias and reporting bias). Authors stated that the study was carried out in 30 clinical sites but neither the sites nor the clinical investigators were identified.

Based on the above reasons (further details are found in [Summary of findings 1](#) and [Summary of findings 2](#)), there was low-certainty of evidence that emixustat and fenretinide had an effect on BCVA and progression of geographic atrophy compared to placebo within the duration of the identified trials (longest: 2 years). The evidence on the adverse effects associated with emixustat are of moderate-certainty due to the relatively large number of participants involved in a well conducted phase 2b/3 study ([SEATTLE Study](#)). However, the reported adverse effects associated with fenretinide are of low-certainty due to the high dropout rate in the fenretinide arms, incomplete reporting and potential confounding effects.

Conflicts of interest were unclear in all three studies. Only one of the six authors in [Dugel 2015](#) seems to be independent of Acucela Inc., which was the company funding the study. In [SEATTLE Study](#), Acucela Inc. participated in all aspects of the study (design, conduct, data collection, data management, data analysis, data interpretation and preparation, review and approval of the manuscript). Five of the six authors in [Mata 2013](#) were either employees or stockholders of ReVision Therapeutics Inc. or Sirion Therapeutics Inc., or both. These companies funded the study. The other author is the founder of Retina Associates of Cleveland, which received grant support from both companies for this trial.

Potential biases in the review process

We followed standard methods expected by Cochrane. There were no potential biases in the review process of which we are aware. We have documented all departures from the protocol in [Differences between protocol and review](#).

Agreements and disagreements with other studies or reviews

This review found that the investigated visual cycle modulators (emixustat and fenretinide) had no significant therapeutic effect on both anatomical (change in lesion size) and visual (BCVA) outcomes in people with geographic atrophy secondary to AMD. The quality of evidence regarding the efficacy of emixustat is of low-certainty based mainly on a phase 2b/3 RCT ([SEATTLE Study](#)). The quality of evidence for fenretinide is of low-certainty based on only one phase 2a RCT ([Mata 2013](#)) with high risk of selective reporting bias. Adverse effects of both drugs are mainly ocular in nature, with delayed dark adaptation and chromatopsia being the most frequently reported events. These adverse events were also the primary factors leading to study withdrawals among participants in the treatment arms. The quality of evidence on adverse effects of both drugs is of moderate-certainty.

Our findings are similar to those in a recent Health Technology Assessment (HTA) review ([Vaugh 2018](#)) and a review conducted by [Hussain 2018a](#). Both studies reviewed the results of visual cycle modulators in geographic atrophy due to AMD and Stargardt disease. However, the [SEATTLE Study](#) RCT was not included in the HTA systematic review. While [Hussain 2018a](#) included this RCT, it did not highlight that participants treated with higher doses

of emixustat had lower incidence of CNV compared to placebo, although the significance of this difference is unclear. It is also worth noting that 60% of the participants who developed CNV in [SEATTLE Study](#) were considered 'high risk' due to previous history of CNV in the non-study eye.

Previous work on human RPE cell lines and rats ([Iriyama 2006](#); [Iriyama 2008](#)) suggests that A2E formation could be implicated in the pathogenesis of CNV secondary to AMD. However, a small observational study of patients with AMD newly diagnosed with CNV using FAF imaging showed that increased FAF signal, indicative of increased lipofuscin in the RPE, was only rarely observed in eyes with CNV and in fellow eyes, suggesting that lipofuscin may not play an essential role in the development of CNV ([McBain 2007](#)). Hence, the reasons behind the potentially reduced incidence of CNV in the participants treated with emixustat and fenretinide - if this were to be confirmed - remain unclear.

AUTHORS' CONCLUSIONS

Implications for practice

Current evidence suggests visual cycle modulators are not effective at reducing the growth of established geographic atrophy in people with AMD.

Implications for research

The design of the trials may not have been optimal. They recruited participants with established and, most often, large areas of macular atrophy. It is possible that, at the time treatment was started, the disease process was too well advanced to halt it ([Schaal 2016](#)).

Future research could consider using visual cycle modulators in earlier stages of AMD (i.e. intermediate AMD), especially in those individuals at higher risk of developing advanced AMD, to determine its potential for suppressing or delaying the occurrence of geographic atrophy or neovascular AMD. The reduction in incidence of CNV formation in participants treated with visual cycle modulators seen in [SEATTLE Study](#) and [Mata 2013](#) would support this type of study. However, caution must be taken regarding the ocular adverse events associated with the mechanisms of action of visual cycle modulators as these may likely affect drug compliance and would be needed to be taken into consideration in power calculations of potential clinical trials with emixustat and fenretinide. Given the high withdrawal rates of participants in the emixustat and fenretinide cohorts compared to placebo, treatment-emergent adverse events leading to discontinuation of study treatment can be utilised as a safety outcome as well in future trials.

It is also important that trials evaluating new treatments for geographic atrophy due to AMD consider the inclusion of outcomes that may be able to provide functional information beyond central vision. Thus, measuring macular sensitivity (using macular microperimetry or central automated visual field testing) would be crucial in future trials as people with early AMD have been shown with macular microperimetry to have reduced macular sensitivity ([Owsley 2000](#); [Owsley 2007](#)). This is supported by histological studies showing significant rod photoreceptor cell loss in early AMD when compared with cone cell loss ([Crucio 1996](#); [Crucio 2000](#)). Other important outcomes such as reading speed, patient reported outcomes and treatment-emergent adverse

events leading to discontinuation of study treatment (Cohen 2019) should be considered when designing clinical trials for new therapies for geographic atrophy due to AMD. Furthermore, the acceptability of new treatments to patients and their cost-effectiveness, in addition to their clinical effectiveness, should be evaluated. As geographic atrophy due to AMD is a slow progressing disease, longer term studies (two years or above) should be considered.

Overall, the pathophysiology of AMD is complex with oxidative damage, chronic inflammation, complement system activation, beta amyloid deposition and lipofuscin formation being implicated (Hussain 2018a). Addressing each of these individually may not be fruitful and a multifaceted approach may be required to treat or prevent geographic atrophy due to AMD.

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REFERENCES

References to studies included in this review

Dugel 2015 {published data only}

Dugel PU, Novack RL, Csaky KG, Richmond PP, Birch DG, Kubota R. Phase 2, randomised, placebo-controlled, 90-day study of emixustat hydrochloride in geographic atrophy associated with dry age-related macular degeneration. *Retina* 2015;**35**(6):1173-83.

Mata 2013 {published data only}

Mata NL, Lichter JB, Vogel R, Han Y, Bui TV, Singerman LJ. Investigation of oral fenretinide for treatment of geographic atrophy in age-related macular degeneration. *Retina* 2013;**33**(3):498-507.

SEATTLE Study {published and unpublished data}

Holz F. Efficacy and safety results from a randomized, controlled, two-year study of emixustat hydrochloride in patients with geographic atrophy secondary to age-related macular degeneration (SEATTLE Study). *Ophthalmologica* 2016;**236**:4.

* Rosenfeld PJ, Dugel PU, Holz FG, Heier JS, Pearlman JA, Novack RL, et al. Emixustat hydrochloride for geographic atrophy secondary to age-related macular degeneration: a randomised clinical trial. *Ophthalmology* 2018;**125**(10):1556-7.

References to studies excluded from this review

Boman 2010 {published data only}

Boman N. Human visual cycle modulation for dry AMD: Novel oral nonretinoid treatment targets visual cycle process that creates toxic byproducts implicated in retinal diseases. *Retina Today* 2010;**October**:76-7.

Additional references

Bavik 2015

Bavik C, Henry SH, Zhang Y, Mitts K, McGinn T, Budzynski E, et al. Visual cycle modulation as an approach toward preservation of retinal integrity. *PLoS One* 2015;**10**(5):e0124940.

Brown 2006

Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *New England Journal of Medicine* 2006;**355**(14):1432-44.

Carmerini 2001

Camerini T, Mariani L, De Palo G, Marubini E, Di Mauro MG, Decensi A, et al. Safety of the synthetic retinoid fenretinide: long-term results from a controlled clinical trial for the prevention of contralateral breast cancer. *Journal of Clinical Oncology* 2001;**19**(6):1664-70.

Charbel Issa 2015

Charbel Issa P, Barnard AR, Herrmann P, Washington I, MacLaren RE. Rescue of the Stargardt phenotype in Abca4

knockout mice through inhibition of vitamin A dimerization. *Proceedings of the National Academy of Sciences of the United States of America* 2015;**112**(27):8415-20.

Cohen 2019

Cohen JA, Comi G, Selmaj KW, Bar-Or A, Arnold DL, Steinman L, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial. *Lancet. Neurology* 2019;**18**(11):1021-33.

Costa 1989

Costa A, Malone W, Perloff M, Buranelli F, Campa T, Dossena G, et al. Tolerability of the synthetic retinoid fenretinide (HPR). *European Journal of Cancer and Clinical Oncology* 1989;**25**(5):805-8.

Crouch 2009

Crouch RK. The visual cycle: generation of 11-cis retinal for photoreceptors. photobiology.info/Crouch.html (accessed 24 July 2018).

Crucio 1996

Crucio C, Medeiros N, Millican C. Photoreceptor loss in age-related macular degeneration. *Investigative Ophthalmology and Visual Science* 1996;**37**(7):1236-49.

Crucio 2000

Crucio C, Owsley C, Jackson G. Spare the rods, save the cones in aging and age-related maculopathy. *Investigative Ophthalmology and Visual Science* 2000;**41**(8):2015-8.

Deeks 2017

Deeks JJ, Higgins JP, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS, editors(s). *Cochrane Handbook for Systematic Reviews of Interventions*. 5.2.0 edition. Cochrane, 2017.

De Palo 1995

De Palo G, Veronesi U, Marubini E, Camerini T, Chiesa F, Nava M, et al. Controlled clinical trials with fenretinide in breast cancer, basal cell carcinoma and oral leukoplakia. *Journal of Cellular Biochemistry* 1995;**22**(Suppl):11-7.

Dobri 2013

Dobri N, Qin Q, Kong J, Yamamoto K, Liu Z, Moiseyev G, et al. A1120, a nonretinoid RBP4 antagonist, inhibits formation of cytotoxic bisretinoids in the animal model of enhanced retinal lipofuscinogenesis. *Investigative Ophthalmology and Visual Science* 2013;**54**(1):85-95.

Domalpally 2016

Domalpally A, Danis R, Agron E, Blodi B, Clemons T, Chew E, et al. Evaluation of geographic atrophy from color photographs and fundus autofluorescence images: Age-Related Eye Disease Study 2 report number 11. *Ophthalmology* 2016;**123**(11):2401-07.

Dorey 1989

Dorey CK, Wu G, Ebenstein D, Garsd A, Weiter JJ. Cell loss in the aging retina. Relationship to lipofuscin accumulation and macular degeneration. *Investigative Ophthalmology and Visual Science* 1989;**30**(8):1691-9.

Egger 1997

Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629-34.

Ferris 2013

Ferris FL 3rd, Wilkinson CP, Bird A, Chakravarthy U, Chew E, Csaky K, et al. Clinical classification of age-related macular degeneration. *Ophthalmology* 2013;**120**(4):844-51.

Fleckenstein 2017

Fleckenstein M, Mitchell P, Freund KB, Sadda S, Holz FG, Brittain C, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology* 2017;**125**(3):369-90.

Gale 2019

Gale RP, Mahmood S, Devonport H, Patel PJ, Ross AH, Walters G, et al. Action on neovascular age-related macular degeneration (nAMD): recommendations for management and service provision in the UK hospital eye service. *Eye* 2019;**33**(1):1-21.

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Version accessed 5 September 2019. Hamilton (ON): McMaster University (developed by Evidence Prime). Available at gradepro.org.

Guyatt 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**:924-6.

Guymer 2019

Guymer RH, McGuinness M, Hodgson LA, Luu CD, Wu Z. Nascent geographic atrophy as a surrogate endpoint in age-related macular degeneration. *Investigative Ophthalmology and Visual Science* 2019;**60**(9):2214.

Hanus 2016

Hanus J, Zhao F, Wang S. Current therapeutic developments in atrophic age-related macular degeneration. *British Journal of Ophthalmology* 2016;**100**(1):122-7.

Higgins 2019

Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Holz 2001

Holz FG, Bellman C, Staudt S, Schutt F, Volcker HE. Fundus autofluorescence and development of geographic atrophy in

age-related macular degeneration. *Investigative Ophthalmology and Visual Science* 2001;**42**(5):1051-6.

Holz 2007

Holz FG, Bindewald-Wittich A, Fleckenstein M, Dreyhaupt J, Scholl HP, Schmitz-Valckenberg S, et al. Progression of geographic atrophy and impact of fundus autofluorescence patterns in age-related macular degeneration. *American Journal of Ophthalmology* 2007;**143**(3):463-72.

Hussain 2018a

Hussain RM, Gregori NZ, Ciulla TA, Lam BL. Pharmacotherapy of retinal disease with visual cycle modulators. *Expert Opinion in Pharmacotherapy* 2018;**19**(5):471-81.

Hussain 2018b

Hussain RM, Ciulla TA, Berrocal AM, Gregori NZ, Flynn HW Jr, Lam BL. Stargardt macular dystrophy and evolving therapies. *Expert Opinion on Biological Therapy* 2018;**18**(10):1049-59.

Iriyama 2006

Iriyama A, Yanagi Y, Inoue Y, Takahashi H, Tamaki Y. Role of A2E in the pathogenesis of CNV. *Investigative Ophthalmology and Visual Science* 2006;**47**(13):41-6.

Iriyama 2008

Iriyama A, Fujiki R, Inoue Y, Takahashi H, Tamaki Y, Takezawa S et al. A2E, a pigment of the lipofuscin of retinal pigment epithelial cells, is an endogenous ligand for retinoic acid receptor. *Journal of Biological Chemistry* 2008;**283**(18):11947-53.

Joachim 2015

Joachim N, Mitchell P, Burlutsky P, Kifley A, Wang JJ. The incidence and progression of age-related macular degeneration over 15 years: the Blue Mountains Eye Study. *Ophthalmology* 2015;**122**(12):2482-9.

Kiser 2014

Kiser PD, Golczak M, Palczewski K. Chemistry of the retinoid (visual) cycle. *Chemical Reviews* 2014;**114**(1):194-232.

Klein 2007

Klein R, Klein BE, Knudtson MD, Meuer SM, Swift M, Gangnon RE. Fifteen-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study. *Ophthalmology* 2007;**114**(2):253-62.

Klein 2008

Klein R, Meuer SM, Knudtson MD, Klein BE. The epidemiology of progression of pure geographic atrophy: the Beaver Dam Eye Study. *American Journal of Ophthalmology* 2008;**146**(5):692-9.

Lamoureux 2011

Lamoureux EL, Mitchell P, Rees G, Cheung G, Yeo L, Lee SY, et al. Impact of early and late age-related macular degeneration on vision-specific functioning. *British Journal of Ophthalmology* 2011;**95**(5):666-70.

Lim 2012

Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY. Age-related macular degeneration. *Lancet* 2012;**379**(9827):1728-38.

Lindblad 2009

Lindblad AS, Lloyd PC, Clemons TE, Gensler GR, Ferris FL 3rd, Klein ML, et al. Change in area of geographic atrophy in the Age-Related Eye Disease Study: AREDS report number 26. *Archives of Ophthalmology* 2009;**127**(9):1168-74.

Lois 2002

Lois N, Owens SL, Coco R, Hopkins J, Fitzke FW, Bird AC. Fundus autofluorescence in patients with age-related macular degeneration and high risk of visual loss. *American Journal of Ophthalmology* 2002;**133**(3):341-9.

Lu 2017

Lu LJ, Liu J, Adelman RA. Novel therapeutics for Stargardt disease. *Graefe's Archive for Clinical and Experimental Ophthalmology* 2017;**255**(6):1057-62.

Ma 2011

Ma L, Kaufman Y, Zhang J, Washington I. C20-D3-vitamin A slows lipofuscin accumulation and electrophysiological retinal degeneration in a mouse model of Stargardt disease. *Journal of Biological Chemistry* 2011;**286**(10):7966-74.

Maeda 2011

Maeda A, Golczak M, Chen Y, Okano K, Kohno H, Shiose S, et al. Primary amines protect against retinal degeneration in mouse models of retinopathies. *Nature Chemical Biology* 2011;**8**(2):170-8.

McBain 2007

McBain VA, Townend J, Lois N. Fundus autofluorescence in exudative age-related macular degeneration. *British Journal of Ophthalmology* 2007;**91**(4):491-6.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *PLoS Medicine* 6;**7**:e1000097. [DOI: [10.1371/journal.pmed1000097](https://doi.org/10.1371/journal.pmed1000097)]

Moseley 2011

Moseley J. Visual function endpoints: The regulatory perspective. EMA Scientific advice and protocol 27 October 2011.

Owsley 2000

Owsley C, Jackson G, Cideciyan A, Huang Y, Fine S, Ho A, et al. Psychophysical evidence for rod vulnerability in age-related macular degeneration. *Investigative Ophthalmology and Visual Science* 2000;**41**(1):267-73.

Owsley 2007

Owsley C, McGwin G, Jackson G, Kallies K, Clark M. Cone- and rod-mediated dark adaptation impairment in age-related maculopathy. *Ophthalmology* 2007;**114**(9):1728-35.

Petrukhin 2007

Petrukhin K. New therapeutic targets in atrophic age-related macular degeneration. *Expert Opinion on Therapeutic Targets* 2007;**11**(5):625-39.

Petrukhin 2013

Petrukhin K. Pharmacological inhibition of lipofuscin accumulation in the retina as a therapeutic strategy for dry AMD treatment. *Drug Discovery Today: Therapeutic Strategies* 2013;**10**(1):e11-e20.

Radu 2005

Radu RA, Han Y, Bui TV, Nusinowitz S, Bok D, Lichter J, et al. Reductions in serum vitamin A arrest accumulation of toxic retinal fluorophores: a potential therapy for treatment of lipofuscin-based retinal diseases. *Investigative Ophthalmology and Visual Science* 2005;**46**(12):4393-401.

Rein 2006

Rein DB, Zhang P, Wirth KE, Lee PP, Hoerger TJ, McCall N, et al. The economic burden of major adult visual disorders in the United States. *Archives of Ophthalmology* 2006;**124**(12):1754-60.

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rosenfeld 2006

Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. *New England Journal of Medicine* 2006;**355**(14):1419-31.

Schaal 2016

Schaal KB, Rosenfeld PJ, Gregori G, Yehoshua Z, Feuer WJ. Anatomic clinical trial endpoints for nonexudative age-related macular degeneration. *Ophthalmology* 2016;**123**(5):1060-79.

Schmitz-Valckenberg 2004

Schmitz-Valckenberg S, Bultmaan S, Dreyhaupt J, Bindewald A, Holz FG, Rohrschneider K. Fundus autofluorescence and fundus perimetry in the junctional zone of geographic atrophy in patients with age-related macular degeneration. *Investigative Ophthalmology and Visual Science* 2004;**45**(12):4470-6.

Schmitz-Valckenberg 2016

Schmitz-Valckenberg S, Sahel JA, Danis R, Fleckenstein M, Jaffe GJ, Wolf S, et al. Natural history of geographic atrophy progression secondary to age-related macular degeneration (geographic atrophy progression study). *Ophthalmology* 2016;**123**(2):361-8.

Scholl 2019

Scholl HP, Tsang SH, Kay CN, Connor TB, Gorin MB, Bernstein PS, et al. Stargardt disease ALK-001 phase 2 clinical trial: 12-month interim data. *Investigative Ophthalmology and Visual Science* 2019;**60**(9):ARVO E-abstract 1336.

Schünemann 2017

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Akl E, et al, on behalf of the Cochrane GRADEing Methods Group and the Cochrane Statistical Methods Group. Chapter 11: Completing 'Summary of findings' tables and grading the confidence in or quality of the evidence. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors), Cochrane

Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017). Cochrane, 2017. Available from www.training.cochrane.org/handbook.

Sears 2017

Sears AE, Bernstein PS, Cideciyan AV, Hoyng C, Charbel Issa P, Palczewski K, et al. Towards treatment of Stargardt disease: workshop organized and sponsored by the foundation fighting blindness. *Translational Vision Science and Technology* 2017;**6**(5):6.

Sparrow 2003

Sparrow JR, Fishkin N, Zhou J, Cai B, Jang YP, Krane S, et al. A2E, a byproduct of the visual cycle. *Vision Research* 2003;**43**(28):2983-90.

Spooner 2018

Spooner KL, Mhlanga CT, Hong TH, Broadhead GK, Chang AA. The burden of neovascular age-related macular degeneration: a patient's perspective. *Clinical Ophthalmology* 2018;**12**:2483-91.

Sterne 2017

Sterne JA, Egger M, Moher D, Boutron I (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors), Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017), Cochrane, 2017. Available from www.training.cochrane.org/handbook.

Sunness 1995

Sunness JS, Schuchard RA, Shen N, Rubin GS, Dagnelie G, Haselwood DM. Landmark-driven fundus perimetry using the scanning laser ophthalmoscope. *Investigative Ophthalmology and Visual Science* 1995;**36**(9):1863-74.

Sunness 1999

Sunness JS, Gonzalez-Baron J, Applegate CA, Bressler NM, Tian Y, Hawkins B, et al. Enlargement of atrophy and visual acuity loss in the geographic atrophy form of age-related macular degeneration. *Ophthalmology* 1999;**106**(9):1768-79.

Sunness 2007

Sunness JS, Margalit E, Srikumaran D, Applegate CA, Tian Y, Perry D, et al. The long-term natural history of geographic atrophy from age-related macular degeneration: enlargement of atrophy and implications for interventional clinical trials. *Ophthalmology* 2007;**114**(2):271-7.

Waugh 2018

Waugh N, Loveman E, Colquitt J, Royle P, Yeong JL, Hoad G, et al. Treatments for dry age-related macular degeneration and Stargardt disease: A systematic review. *Health Technology Assessment* 2018;**22**(27):1-168.

WHO 2002

World Health Organization. Causes of blindness and visual impairment. www.who.int/blindness/causes/en/ (accessed prior to 3 August 2018).

Wong 2014

Wong WL, Su X, Li X, Cheung CM, Klein R, Cheng CY, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Global Health* 2014;**2**(2):106-16.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Dugel 2015

Study characteristics

Methods	Parallel group RCT
	Method of allocation: Computer generated randomisation code
	Unit of analysis: 1 study eye per participant
	Number of participants randomised: 77
	Number of participants excluded after randomisation: 5 (change in systemic medication and/or abnormal laboratory or electrocardiogram results)
	Losses to follow-up (29 participants):
	<ul style="list-style-type: none"> • Emixustat 2 mg once in the morning: n = 0 • Emixustat 5 mg once in the morning: n = 2 (adverse event) • Emixustat 5 mg once in the evening: n = 3 (adverse event) • Emixustat 7 mg once in the morning: n = 12 (adverse event: 2; arm discontinued early by sponsor: 10) • Emixustat 10 mg once in the morning: n = 6 (adverse event: 1; arm discontinued early by sponsor: 5)

Dugel 2015 (Continued)

- Placebo: n = 6 (all participants assigned to placebo arms for comparison to emixustat 7 mg once in the morning and 10 mg once in the morning cohorts were discontinued early by sponsor)

n = number of participants

Note: The 7 mg and 10 mg arms together with their respective placebo comparators were discontinued early by sponsors due to initial estimates of the frequency and severity of adverse events.

Reported power calculations: Not provided

Missing data: Intention-to-treat principle. Analyses were performed on all randomised participants who received at least 1 dose of study drug. As stated above, two cohort groups (7 and 10 mg qAM) were discontinued.

Participants

Baseline Characteristics

Geographic atrophy

Emixustat 2 mg once in the morning (n = 12)

- Age, years median (range): 78 (55-88)
- Sex, female n (%): 10 (83.3%)
- Race, white n (%): 11 (91.7%)
- Study eye, right n (%): 6 (50%)
- Study eye, left n (%): 6 (50%)
- BCVA, median (range), letter score: 68 (33-83)
- BCVA, median (range), approximate Snellen equivalent: 20/44 (20/219-20/22)
- GA lesion size, mm², median (range) *based on fundus fluorescein angiography (FFA): 9.61 (0.84-28.77)

Emixustat 5 mg once in the morning (n = 12)

- Age, years median (range): 75.5 (60-89)
- Sex, female n (%): 8 (66.7%)
- Race, white n (%): 10 (83.3%)
- Study eye, right n (%): 7 (58.3%)
- Study eye, left n (%): 5 (41.7%)
- BCVA, median (range), letter score: 74 (34-85)
- BCVA, median (range), approximate Snellen equivalent: 20/33 (20/209-20/20)
- GA lesion size, mm², median (range) *based on FFA: 7.38 (2.24-14.34)

Emixustat 5 mg once in the evening (n = 12)

- Age, years median (range): 82 (67-91)
- Sex, female n (%): 8 (66.7%)
- Race, white n (%): 11 (91.7%)
- Study eye, right n (%): 7 (58.3%)
- Study eye, left n (%): 5 (41.7%)
- BCVA, median (range), letter score: 58.5 (30-84)
- BCVA, median (range), approximate Snellen equivalent: 20/68 (20/250-20/21)
- GA lesion size, mm², median (range) *based on FFA: 11.77 (0.68-31.01)

Emixustat 7 mg once in the morning (n = 12)

- Age, years median (range): 79 (65-95)
- Sex, female n (%): 7 (58.3%)
- Race, white n (%): 12 (100%)
- Study eye, right n (%): 7 (58.3%)
- Study eye, left n (%): 5 (41.7%)

Dugel 2015 (Continued)

- BCVA, median (range), letter score: 52.5 (19-74)
- BCVA, median (range), approximate Snellen equivalent: 20/89 (20/418-20/33)
- GA lesion size, mm², median (range) *based on FFA: 9.37 (4.79-23.42)

Emixustat 10 mg once in the morning (n = 6)

- Age, years median (range): 77 (73-85)
- Sex, female n (%): 4 (67.7%)
- Race, white n (%): 6 (100%)
- Study eye, right n (%): 2 (33.3%)
- Study eye, left n (%): 4 (66.7%)
- BCVA, median (range), letter score: 60 (18-85)
- BCVA, median (range), approximate Snellen equivalent: 20/63 (20/438-20/20)
- GA lesion size, mm², median (range) *based on FFA: 7.47 (5.36-25.56)

All emixustat (n = 54)

- Age, years median (range): 78.5 (55-95)
- Sex, female n (%): 37 (68.5%)
- Race, white n (%): 50 (92.6%)
- Study eye, right n (%): 29 (53.7%)
- Study eye, left n (%): 25 (46.3%)
- BCVA, median (range), letter score: 63 (18-85)
- BCVA, median (range), approximate Snellen equivalent: 20/55 (20/438-20/20)
- GA lesion size, mm², median (range) *based on FFA: 8.98 (0.68-31.01)

Placebo (n = 18)

- Age, years median (range): 82 (55-87)
- Sex, female n (%): 10 (55.6%)
- Race, white n (%): 17 (94.4%)
- Study eye, right n (%): 9 (50%)
- Study eye, left n (%): 9 (50%)
- BCVA, median (range), letter score: 65 (40-79)
- BCVA, median (range), approximate Snellen equivalent: 20/50 (20/160-20/26)
- GA lesion size, mm², median (range) *based on FFA: 8.23 (0.16-23.13)

n = number of participants

Equivalence of baseline characteristics: No

Note: The pooled emixustat group had a slightly lower median age (78.5 years vs. 82 years) and a larger proportion of female participants (68.5% vs. 55.6%) when compared with the placebo group. The median lesion size, as assessed by FA, was 8.98 mm² (range 0.68–31.01mm²) for the pooled emixustat participants compared with 8.23 mm² (range 0.16–23.13 mm²) for the placebo group.

Inclusion criteria:

- Adults with a clinical diagnosis of geographic atrophy, as defined by well-demarcated areas of partial or complete RPE depigmentation or loss that was confirmed by a central reading centre
- BCVA equal to or better than 20/400 in the study eye

Exclusion criteria:

- GA in either eye associated with ocular disease other than AMD
- Known congenital/inherited colour vision abnormalities
- Active exudative AMD or current treatment for exudative AMD in study eye
- Cataract or other intraocular surgery within 3 months

Dugel 2015 (Continued)

- Laser-assisted in situ keratomileusis (LASIK) surgery, glaucoma filtration surgery, or corneal transplant within 6 months of study entry in either eye
- Active ocular disease or clinically significant ocular abnormalities in either eye that would interfere with study evaluation

Other information about entry criteria: It is stated that twelve participants (10 emixustat and 2 placebo) were granted exemptions to entry criteria due primarily to changes in medication before study dosing that could be permitted on an individual basis per protocol.

Interventions

Intervention Characteristics

Emixustat 2 mg once in the morning (n = 12)

- *Duration of intervention:* 90 days
- *Dose:* 2 mg, once daily in the morning
- *Route of administration:* Oral
- *Number of participants completed 90 day study period:* 12

Emixustat 5 mg once in the morning (n = 12)

- *Duration of intervention:* 90 days
- *Dose:* 5 mg, once daily in the morning
- *Route of administration:* Oral
- *Number of participants completed 90 day study period:* 10

Emixustat 5 mg once in the evening (n = 12)

- *Duration of intervention:* 90 days
- *Dose:* 5 mg, once daily in the evening
- *Route of administration:* Oral
- *Number of participants completed 90 day study period:* 9

All emixustat (n = 54)

- *Duration of intervention:* 90 days
- *Dose:* N/A
- *Route of administration:* Oral
- *Number of participants completed 90 day study period:* 31

Placebo (n = 18)

- *Duration of intervention:* 90 days
- *Dose:* once daily, in the morning or evening (for 5 mg qPM cohort)
- *Route of administration:* Oral
- *Number of participants completed 90 day study period:* 12

n = number of participants

Participants completing the study: Only 31 emixustat participants (57%) and 12 placebo participants (67%) completed the study as planned.

Outcomes

Primary outcome: not specified

Secondary outcomes: not specified

Outcomes reported in manuscript:

- Adverse events
- Mean rod b-wave recovery rate post-photobleaching
- Cone response on electroretinogram (ERG) (30-Hz flicker and single-flash amplitudes)

Dugel 2015 (Continued)

- Mean GA lesion size change from baseline (as measured by colour fundus photography [CFP], fundus autofluorescence [FAF] imaging and FFA)

Follow-up period: 90 days and 7-14 days after cessation of emixustat/placebo

Full-field ERG procedures were performed on both eyes of each participant throughout study according to the International Society for Clinical Electrophysiology of Vision (ISCEV) protocol. ERG measurements were taken at baseline, days 14, 60, 90 and at study exit (7-14 days after cessation of emixustat/placebo).

Note: 5 mg once in the morning cohort had further ERG measurements on days 7 and 30 in addition to the follow-up visits above.

Notes

Trial ID: clinicaltrials.gov registration number - NCT01002950

Date of recruitment of participants: December 2009 to June 2012

Source of funding: Acucela Inc. Only one of the six authors seems to be independent of Acucela Inc. (three of the six authors are paid advisors for Acucela, one is the Chairman of the Board of Acucela). There is no reference with regards to the sixth author.

Trial authors were contacted to clarify queries regarding data. No response was given despite 2 attempts.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Dose arms were sequentially enrolled and participants were randomly assigned using a computer-generated randomisation code
Allocation concealment (selection bias)	Low risk	Randomisation code was kept under 'lock and key'.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was double-masked within each arm to avoid bias, and emixustat and placebo tablets were identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study was double-masked.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 59.7% of participants (31 emixustat and 12 placebo) completed the 90 day study as planned. 8 participants that received emixustat discontinued study drug due to adverse events. The 7 mg and 10 mg dose arms were discontinued by the sponsor early because of initial estimates of frequency and severity of adverse events, which led to discontinuation of an additional 15 emixustat participants (28%) and 6 placebo participants (33%). Numbers and reasons provided, imbalance between groups. Median exposure to emixustat in the 7 mg and 10 mg arms was 25 days each compared to 90 days in other treatment arms.
Selective reporting (reporting bias)	High risk	Not all outcome data is fully reported with summary statements rather than point estimates and measures of variability. Pharmacokinetics stated as an outcome in the trial registry record but not reported. Not all ocular adverse events were reported (only events that have 2 or more participants affected in the total emixustat cohort were reported in the manuscript). Adverse events occurring in 1 participant would not have been included in the provided table in the paper.

Dugel 2015 (Continued)

Other bias	Low risk	There were no other potential sources of bias.
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Mata 2013
Study characteristics

Methods	<p>Parallel group RCT</p> <p>Method of allocation: Not reported</p> <p>Unit of analysis: 1 study eye per participant</p> <p>Number of participants randomised: 246</p> <p>Number of participants excluded after randomisation: 0</p> <p>Losses to follow-up (n = 68):</p> <ul style="list-style-type: none"> Fenretinide 100 mg: n = 28 (withdrew consent: 12; lost to follow-up: 2; adverse event 14) Fenretinide 300 mg: n = 26 (withdrew consent: 8; protocol violation: 1; adverse event 17) Placebo: n = 14 (withdrew consent: 8; protocol violation: 1; adverse event: 5) <p>n = number of participants</p> <p>Reported power calculations: No</p> <p>Missing data: Intent-to-treat analysis for lesion growth rate</p> <p>Imputation for missing data were not used.</p> <p>Safety analyses were performed in all randomised participants who received at least 1 dose of study drug/placebo.</p> <p>Lesion growth analyses were performed on all randomised participants who received at least 1 dose of study drug/placebo, who had at least 2 follow-up visits past 6 months and who had completed at least 18 months of treatment.</p>
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Participants

Baseline Characteristics

Fenretinide 100 mg (n = 80)

- Age, years median (range): 79.5 (58-89)
- Sex, female n (%): 52 (65%)
- Race, white n (%): 80 (100%)
- BCVA, mean, letter score: 68.59
- GA lesion size, mm², median (SD) *based on colour fundus photography (CFP): 8.10 (4.78)
- GA lesion size, mm², median (SD) *based on fundus autofluorescence (FAF) imaging: 8.33 (5.10)

Fenretinide 300 mg (n = 84)

- Age, years median (range): 79 (53-90)
- Sex, female n (%): 45 (53.6%)
- Race, white n (%): 83 (98.8%)
- BCVA, mean, letter score: 68.12
- GA lesion size, mm², median (SD) *based on CFP: 9.06 (5.03)
- GA lesion size, mm², median (SD) *based on FAF: 9.02 (5.26)

Placebo (N = 82)

Mata 2013 (Continued)

- Age, years median (range): 80 (55-89)
- Sex, female n (%): 52 (63.4%)
- Race, white n (%): 81 (98.8%)
- BCVA, mean, letter score: 66.57
- GA lesion size, mm², median (SD) *based on CFP: 8.17 (4.50)
- GA lesion size, mm², median (SD) *based on FAF: 8.55 (4.84)

n = number of participants

Equivalence of baseline characteristics: Yes

Note: The authors reported that the study population was demographically and clinically comparable across all three groups, with no significant difference in baseline BCVA or lesion sizes. However, it was also reported that the fenretinide 300 mg arm had a higher percentage of patients with geographic atrophy lesions that involved or encroached upon the fovea at baseline (81%), compared to the fenretinide 100 mg arm (72%) and the placebo arm (70%). The significance of this is unclear.

Inclusion criteria:

- 50-89 years old male or female
- Geographic atrophy (secondary to dry AMD) within 500 µm of fovea
- Total atrophic area 1-8 disk areas (2.54 to 20.32 mm²) not characterised as either focal or patchy by AF photography
- BCVA of 20/20 to 20/100 (Snellen equivalent using Early Treatment Diabetic Retinopathy Study [ET-DRS] chart)

Exclusion criteria:

- People with active CNV in the study eye (a history of CNV in either eye was allowed)

Interventions
Intervention Characteristics

Fenretinide 100 mg (n = 80)

- Duration of intervention: 24 months
- Dose: 100 mg, Once daily, 30 minutes after evening meal
- Route of administration: Oral
- Number of participants completed 24 months study period: 52

Fenretinide 300 mg (n = 84)

- Duration of intervention: 24 months
- Dose: 300 mg, Once daily, 30 minutes after evening meal
- Route of administration: Oral
- Number of participants completed 24 months study period: 58

Placebo (n = 82)

- Duration of intervention: 24 months
- Dose: Once daily, 30 minutes after evening meal
- Route of administration: Oral
- Number of participants completed 24 months study period: 68

n = number of participants

Outcomes

Primary outcome: not specified

Secondary outcome: not specified

Outcomes reported in manuscript:

Mata 2013 (Continued)

- Adverse events
- Mean change in BCVA from baseline at 24 months
- Mean percentage change in delayed dark adaptation grade
- Median geographic atrophy lesion growth rate (mm²/year) as measured by CFP
- Incidence of CNV onset in study/fellow eye
- Serum retinol-binding protein (RBP) levels

Follow-up period: 1 month after study drug discontinued at month 24.

BCVA assessed at baseline, months 1, 3, 6, 12, 18, 24 and 25.

Delayed dark adaptation was assessed at baseline, months 1, 6, 12 and 24.

Serum RBP levels assessed at baseline, months 1, 3, 6, 12, 18, 24 and 25.

Notes	<p>Trial ID: clinicaltrials.gov registration number - NCT00429936</p> <p>Date of recruitment of participants: December 2006 to May 2010</p> <p>Source of funding: ReVista Therapeutics Inc., Sirion Therapeutics Inc. Five of the six authors were either employees or stockholders of ReVista Therapeutics Inc. or Sirion Therapeutics Inc. or both, and these two companies funded the study. The other author is the founder of Retina Associates of Cleveland, which received grant support from both companies for this trial.</p> <p>We contacted trial authors to clarify queries regarding data. Corresponding author responded but was unable to clarify queries without establishing a consulting contract.</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Manuscript stated participants are randomly assigned with a 1:1:1 ratio but no further details regarding how randomisation was achieved
Allocation concealment (selection bias)	Unclear risk	No information about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was double-masked.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Baseline retinal images (CFP, FAF and FFA) were evaluated by masked readers. OCT data evaluated by a separate masked reading centre. Hence, the results of the efficacy of the study drug, reported as annualised lesion growth rate will have a low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	There was early withdrawal from the study in 35% and 31% of patients in the fenretinide 100 mg and fenretinide 300 mg groups respectively, much higher compared to the placebo arm (17.1%). There was no attempt to evaluate statistically if the patients that were retained in the study were in any way different than those who withdrew. Authors also stated efficacy analysis was on intention-to-treat basis defined as all randomised participants who received at least one dose and had at least 2 follow-up visits. Annual lesion growth analysis was only performed for patients completing at least 18 months of treatment.
Selective reporting (reporting bias)	High risk	OCT outcomes (retinal thickness and macular volume) are not reported. Distribution of participants with history of CNV in study eye not reported. Authors provided values of incidence of CNV but this was not a planned outcome mea-

Mata 2013 (Continued)

sure (not provided in the methods section). Systemic adverse events reported but no specific description. The analysis of annual lesion growth rate as a function of levels of serum RBP was not pre-specified in the methodology section nor in the trial registry record. Median annual growth rate of GA lesion measured by FAF not reported. It is only summarised as having excellent agreement with data from colour fundus photography. We are unsure if all participants or only those who completed at least 18 months of the study are included in visual acuity analysis.

Other bias	Low risk	No other potential sources of bias
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SEATTLE Study
Study characteristics

Methods	<p>Parallel Group RCT</p> <p>Method of allocation: Interactive web response system</p> <p>Unit of analysis: 1 study eye per participant</p> <p>Number of participants randomised: 508</p> <p>Number of participants excluded after randomisation: 5 (Did not take study drug)</p> <ul style="list-style-type: none"> • Emixustat 2.5 mg: n = 1 • Emixustat 5 mg: n = 1 • Emixustat 10 mg: n = 0 • Placebo: n = 3 <p>Sample size estimated: 480 participants to have 80% power to detect significant difference between arms for primary outcome</p> <p>Losses to follow-up (n = 188):</p> <ul style="list-style-type: none"> • Emixustat 2.5 mg: n = 56 (adverse event: 33; withdrew consent: 16; investigator/sponsor decision: 1; lost to follow-up: 2; death: 3; other: 1) • Emixustat 5 mg: n = 54 (adverse event: 44; withdrew consent: 7; death: 2; other: 1) • Emixustat 10 mg: n = 50 (adverse event: 39; withdrew consent: 9, lost to follow-up: 1, death: 1) • Placebo: n = 28 (adverse event: 16; withdrew consent: 7; investigator/sponsor decision: 3; lost to follow-up: 1; other: 1) <p>n = number of participants</p> <p>Missing data: Intention-to-treat analysis</p>
Participants	<p>Baseline Characteristics</p> <p>NL-BCVA; LL-BCVA (measured by placing a 2.0 log unit neutral density filter over the best-correction); LLD ((NL-BCVA score) - (LL-BCVA score))</p> <p>Emixustat 2.5 mg (n = 133)</p> <ul style="list-style-type: none"> • Age at screening (years), mean (SD): 78.2 (7.1) • Sex, female, n (%): 79 (59.4) • Race, white, n (%): 129 (97.0) • Country: United States, n (%); Germany, n (%): 117 (88.0); 16 (12.0) • BMI, kg/m², mean (SD): 28.4 (5.8) • Current/former smoker, n (%): 78 (58.6)

SEATTLE Study (Continued)

- History of hypertension, *n* (%): 91 (68.4)
- History of hypercholesterolaemia, *n* (%): 45 (33.8)
- Iris colour, blue, *n* (%): 58 (43.6)
- Total GA lesion size in study eye, mm², mean (SD): 6.7 (3.7)
- Multifocal GA lesion in study eye, *n* (%): 93 (69.9)
- Presence of RPE atrophy under foveal cent er of study eye by SD OCT, *n* (%): 77 (57.9)
- Presence of GA lesion in non-study eye, *n* (%): 95 (71.4)
- NL-BCVA letter score in study eye: mean (SD); median (range): 65.4 (13.6); 67 (21,95)
- LLD letter score in study eye: mean (SD), median (range): 23.7 (17.2); 20 (-16,80)
- Prior or current CNV in non-study eye at screening, *n* (%): 48 (36.1)

Emixustat 5 mg (*n* = 134)

- Age at screening (years), mean (SD): 78.2 (7.8)
- Sex, female, *n* (%): 72 (53.7)
- Race, white, *n* (%): 130 (97.0)
- Country: United States, *n* (%); Germany, *n* (%): 118 (88.1); 16 (11.9)
- BMI, kg/m², mean (SD): 27.9 (4.7)
- Current/former smoker, *n* (%): 71 (53.0)
- History of hypertension, *n* (%): 81 (60.4)
- History of hypercholesterolaemia, *n* (%): 49 (36.6)
- Iris colour, blue, *n* (%): 55 (41.0)
- Total GA lesion size in study eye, mm², mean (SD): 7.0 (3.9)
- Multifocal GA lesion in study eye, *n* (%): 89 (66.4)
- Presence of RPE atrophy under foveal cent er of study eye by SD OCT, *n* (%): 95 (70.9)
- Presence of GA lesion in non-study eye, *n* (%): 95 (70.9)
- NL-BCVA letter score in study eye: mean (SD); median (range): 66.3 (12.5); 68 (37,89)
- LLD letter score in study eye: mean (SD), median (range): 21.1 (15.1); 20 (-9, 77)
- Prior or current CNV in non-study eye at screening, *n* (%): 37 (27.6)

Emixustat 10 mg (*n* = 103)

- Age at screening (years), mean (SD): 77.2 (8.0)
- Sex, female, *n* (%): 61 (59.2)
- Race, white, *n* (%): 102 (99.0)
- Country: United States, *n* (%); Germany, *n* (%): 95 (92.2); 8 (7.8)
- BMI, kg/m², mean (SD): 28.1 (5.6)
- Current/former smoker, *n* (%): 65 (63.1)
- History of hypertension, *n* (%): 75 (72.8)
- History of hypercholesterolaemia, *n* (%): 40 (38.8)
- Iris colour, blue, *n* (%): 39 (37.9)
- Total GA lesion size in study eye, mm², mean (SD): 7.0 (4.2)
- Multifocal GA lesion in study eye, *n* (%): 69 (67.0)
- Presence of RPE atrophy under foveal cent er of study eye by SD OCT, *n* (%): 67 (65.0)
- Presence of GA lesion in non-study eye, *n* (%): 75 (72.8)
- NL-BCVA letter score in study eye: mean (SD); median (range): 66.7 (12.7); 70 (34,89)
- LLD letter score in study eye: mean (SD), median (range): 22.6 (17.5); 19 (-3,76)
- Prior or current CNV in non-study eye at screening, *n* (%): 36 (35.0)

All emixustat (*n* = 370)

- Age at screening (years), mean (SD): N/A
- Sex, female, *n* (%): 212 (57.3)
- Race, white, *n* (%): 361 (97.6)

SEATTLE Study (Continued)

- Country: United States, n (%); Germany, n (%): 330 (89.2)
- BMI, kg/m², mean (SD): 40 (10.8)
- Current/former smoker, n (%): 214 (57.8)
- History of hypertension, n (%): 247 (66.8)
- History of hypercholesterolaemia, n (%): 134 (36.2)
- Iris colour, blue, n (%): 152 (41.1)
- Total GA lesion size in study eye, mm², mean (SD): N/A
- Multifocal GA lesion in study eye, n (%): 251 (67.8)
- Presence of RPE atrophy under foveal cent er of study eye by SD OCT, n (%): 239 (64.6)
- Presence of GA lesion in non-study eye, n (%): 265 (71.6)
- NL-BCVA letter score in study eye: mean (SD); median (range): N/A
- LLD letter score in study eye: mean (SD), median (range): N/A
- Prior or current CNV in non-study eye at screening, n (%): 121 (32.7)

Placebo (n = 133)

- Age at screening (years), mean (SD): 77.1 (8.1)
- Sex, female, n (%): 75 (56.4)
- Race, white, n (%): 129 (97.0)
- Country: United States, n (%); Germany, n (%): 116 (87.2); 17 (12.8)
- BMI, kg/m², mean (SD): 28.4 (6.6)
- Current/former smoker, n (%): 73 (54.9)
- History of hypertension, n (%): 86 (64.7)
- History of hypercholesterolaemia, n (%): 42 (31.6)
- Iris colour, blue, n (%): 46 (34.6)
- Total GA lesion size in study eye, mm², mean (SD): 7.0 (4.1)
- Multifocal GA lesion in study eye, n (%): 92 (69.2)
- Presence of RPE atrophy under foveal cent er of study eye by SD OCT, n (%): 74 (55.6)
- Presence of GA lesion in non-study eye, n (%): 107 (80.5)
- NL-BCVA letter score in study eye: mean (SD); median (range): 69.0 (13.4); 70 (36,89)
- LLD letter score in study eye: mean (SD), median (range): 23.7 (17.6); 19 (-16,80)
- Prior or current CNV in non-study eye at screening, n (%): 43 (32.3)

Overall

- Age at screening (years), mean (SD): 77.7 (7.7)
- Sex, female, n (%): 287 (57.1)
- Race, white, n (%): 490 (97.4)
- Country: United States, n (%); Germany, n (%): USA--446 (88.7); Germany 57 (11.3)
- BMI, kg/m², mean (SD): N/A
- Current/former smoker, n (%): 287 (57.1)
- History of hypertension, n (%): 333 (66.2)
- History of hypercholesterolaemia, n (%): 176 (35)
- Iris colour, blue, n (%): 198 (39.4)
- Total GA lesion size in study eye, mm², mean (SD): 6.9 (3.9)
- Multifocal GA lesion in study eye, n (%): 343 (68.2)
- Presence of RPE atrophy under foveal cent er of study eye by SD OCT, n (%): 313 (62.2)
- Presence of GA lesion in non-study eye, n (%): 372 (74)
- NL-BCVA letter score in study eye: mean (SD); median (range): 66.8 (13.1); 69 (21, 95)
- LLD letter score in study eye: mean (SD), median (range): 22.8 (16.8); 20 (-16, 80)
- Prior or current CNV in non-study eye at screening, n (%): 164 (32.6)

n = number of participants

SEATTLE Study (Continued)

Equivalence of baseline characteristics: Yes

Note: There was imbalance on presence of a diffuse pattern of increased autofluorescence, presence of reticular pseudodrusen in the study eye and on age at screening when comparing participants that completed the study and those that were terminated early ($P < 0.05$).

Inclusion criteria:

- 55 years of age or older
- Clinical diagnosis of geographic atrophy secondary to non-exudative AMD in 1 or both eyes
- Study eye has a total GA area of 1.25-18 mm² by blue light (488 nm) fundus autofluorescence (FAF) imaging. If GA is multifocal, then ≥ 1 GA locus was ≥ 1.25 mm²
- Entire lesions should be visualised in a macula-centred image, should not be contiguous with any peripapillary atrophy
- Normal luminance best-corrected visual acuity (NL-BCVA) scores in study eye are ≥ 35 Early Treatment Diabetic Retinopathy Study (ETDRS) letters

Exclusion criteria:

- History of or active CNV associated with AMD in study eye
- GA not associated with AMD in either eye
- Active ocular disease significantly affecting visual function
- History of macular oedema, external beam radiation, macular surgery or transpupillary thermotherapy in the study eye
- History of intraocular or ocular surface surgery in either eye during 3 months before screening
- History of myocardial infarction, stroke, unstable ischaemic heart disease, uncontrolled cardiac arrhythmia or hospitalisation for congestive heart failure within 6 months of screening
- Cancer within 1 year of screening (except non-metastatic in-situ or well-controlled carcinoma)
- Unstable or poorly controlled medical conditions that would interfere with safety evaluation
- Pregnant/lactating females (participants of reproductive potential are to use effective contraception during and for 30 days after treatment)

Interventions

Intervention Characteristics

Emixustat 2.5 mg (n = 133)

- *Duration of intervention:* 24 months
- *Frequency and timing of dosing:* Once a day, every evening
- *Route:* Oral
- *Number of participants completed study :* 78

Emixustat 5 mg (n = 134)

- *Duration of intervention:* 24 months
- *Frequency and timing of dosing:* Once a day, every evening
- *Route:* Oral
- *Number of participants completed study :* 81

Emixustat 10 mg (n = 103)

- *Duration of intervention:* 24 months
- *Frequency and timing of dosing:* Once a day, every evening
- *Route:* Oral
- *Number of participants completed study :* 53

All emixustat (n = 370)

- *Duration of intervention:* 24 months
- *Frequency and timing of dosing:* Once a day, every evening

SEATTLE Study (Continued)

- *Route:* Oral
- *Number of participants completed study :* 212

Note: Doses were fixed for participants receiving 2.5 mg and 5mg emixustat. Doses were titrated from 5mg to 7.5 mg emixustat (after 1 month) to 10 mg emixustat (after 2 months) for participants assigned to 10 mg emixustat. During the month after up-titration to 10 mg, participants who experienced ocular adverse event that investigators determined would lead to discontinuation of treatment could undergo a dose reduction to 5 mg. 22 of these participants reduced their dose from 10 mg to 5 mg during the third month of treatment. Data for this group remains in the 10 mg arm. Participants in both the 2.5 mg and 5 mg arms underwent similar mock titrations to preserve masking.

Placebo (n = 133)

- *Duration of intervention:* 24 months
- *Frequency and timing of dosing:* Once a day, every evening
- *Route:* Oral
- *Number of participants completed study :* 108

Note: Doses were fixed for participants in the placebo arm. They underwent mock titrations as per the emixustat cohorts to preserve blinding.

n = number of participants

Outcomes	<p>Primary outcome:</p> <ul style="list-style-type: none"> • Mean annual growth rate (mm²/year) in total area of GA lesion of study eye as measured by fundus autofluorescence (FAF) imaging <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Mean change from baseline in NL-BCVA of study eye at 24 months • Development of CNV in study eye at any time during the study (24 months) • Adverse events • Changes from baseline in laboratory values, vital signs, physical examination findings, electrocardiograms, ophthalmic assessments (not reported) <p>Follow-up period: 30 days off-drug period after 24 months of intervention</p> <p>Change in total area of GA (mm²) assessed at baseline, then at months 6, 12, 18 and 24.</p> <p>Change in total NL-BCVA score assessed at baseline, then at months 3, 6, 9, 12, 15, 18, 21, 24 and 25.</p>
Notes	<p>Study name: Safety and Efficacy Assessment Treatment Trials of Emixustat hydrochloride (SEATTLE)</p> <p>Trial ID: clinicaltrials.gov registration number - NCT01802866</p> <p>Date of recruitment of participants: February 2013 to April 2016</p> <p>Source of funding: Acucela Inc. Acucela participated in all aspects of the study including design, conduct, data collection, data management, data analysis, data interpretation and preparation, review and approval of the manuscript.</p> <p>We contacted trial authors to clarify queries regarding data. Responses from authors were helpful.</p>
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	<p>Low risk</p> <p>Randomisation was stratified by country using an interactive web response system.</p>

SEATTLE Study (Continued)

Allocation concealment (selection bias)	Low risk	Information was obtained by communicating with the corresponding author. The method used was not reported in the published manuscript. All study medications were supplied in blister-card packaging and all study medication tablets (emixustat and placebo) were identical in appearance and dosages.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Masking was preserved in all arms as mock up and down titrations were identical to 10 mg cohort.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All outcome assessors were masked to the treatment allocation. CNV onset in the study eye was determined by the investigators who were all masked to the treatment allocation. Information was obtained by communicating with the corresponding author.
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout rate mainly due to adverse events. Only 63% of total assigned participants completed the study. 80% of participants in the placebo arm completed the study whereas only 57% of participants combined from all three intervention arms completed the study.
Selective reporting (reporting bias)	Low risk	Primary outcome was fully reported. Main secondary outcomes were fully reported.
Other bias	Low risk	No other potential sources of bias

AMD: age-related macular degeneration
 BCVA: best-corrected visual acuity
 CFP: colour fundus photography
 CNV: choroidal neovascularisation
 FAF: fundus autofluorescence imaging
 FFA: fundus fluorescein angiography
 LL-BCVA: low luminance BCVA
 LLD: low luminance deficit
 NL-BCVA: normal luminance BCVA
 OCT: optical coherence tomography
 RCT: randomised controlled trial

Characteristics of excluded studies [ordered by study ID]

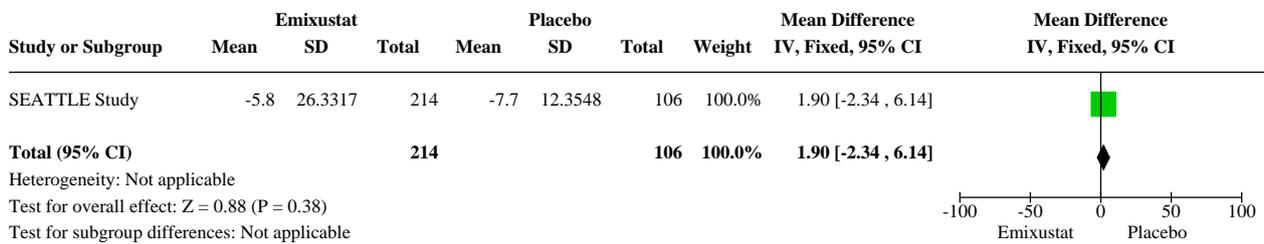
Study	Reason for exclusion
Boman 2010	This is an online editorial regarding use of emixustat in geographic atrophy due to age-related macular degeneration.

DATA AND ANALYSES

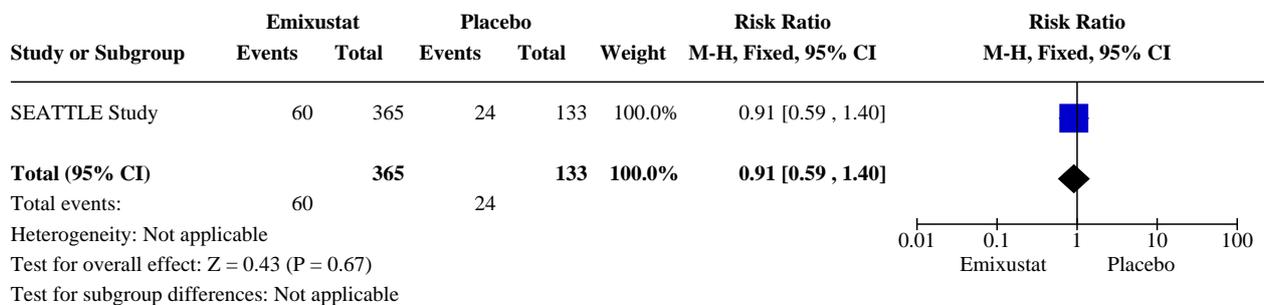
Comparison 1. Emixustat vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Mean change in BCVA from baseline at month 24 (EDTRS letters)	1	320	Mean Difference (IV, Fixed, 95% CI)	1.90 [-2.34, 6.14]
1.2 Incidence of participants losing 15 letters or more at last follow-up visit	1	498	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.59, 1.40]
1.3 Progression of geographic atrophy (mean; mm ² /year)	1	503	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.26, 0.44]
1.4 Mean change in lesion size from baseline at day 90 measured by FAF (mm ²)	1	31	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-2.59, 1.99]
1.5 Mean change in lesion size from baseline at day 90 measured by FFA (mm ²)	1	43	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-1.36, 1.16]
1.6 Mean change in lesion size from baseline at day 90 measured by CFP (mm ²)	1	38	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-1.89, 1.49]
1.7 Incidence of CNV onset	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.28, 1.66]

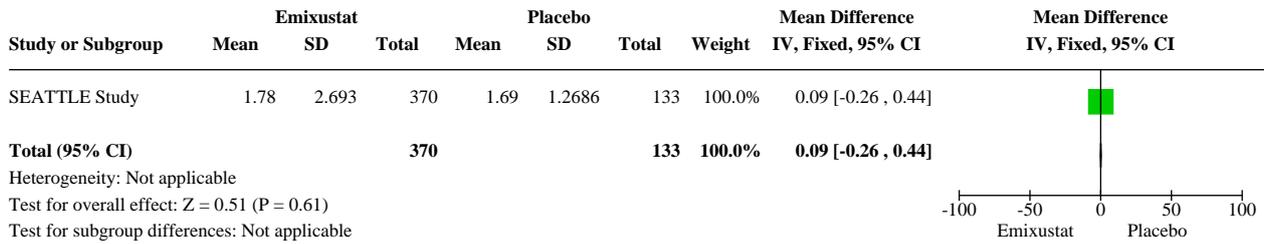
Analysis 1.1. Comparison 1: Emixustat vs placebo, Outcome 1: Mean change in BCVA from baseline at month 24 (EDTRS letters)



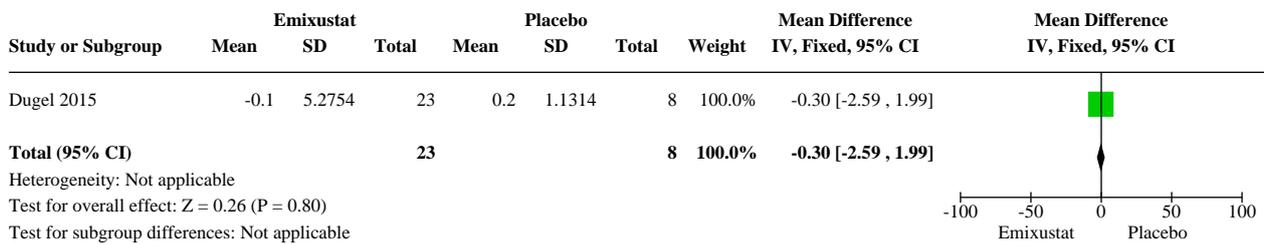
Analysis 1.2. Comparison 1: Emixustat vs placebo, Outcome 2: Incidence of participants losing 15 letters or more at last follow-up visit



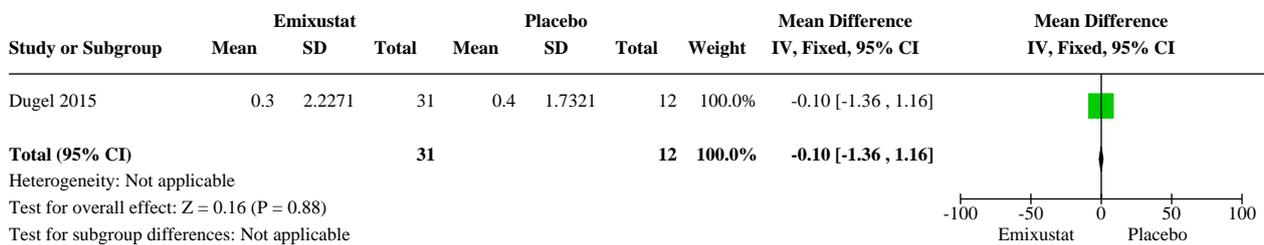
Analysis 1.3. Comparison 1: Emixustat vs placebo, Outcome 3: Progression of geographic atrophy (mean; mm²/year)



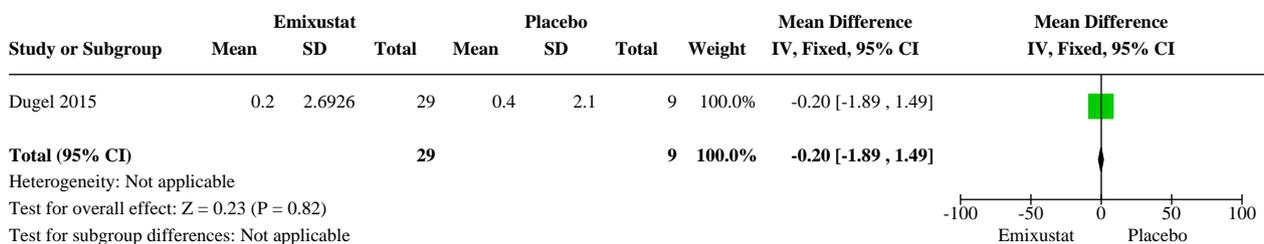
Analysis 1.4. Comparison 1: Emixustat vs placebo, Outcome 4: Mean change in lesion size from baseline at day 90 measured by FAF (mm²)



Analysis 1.5. Comparison 1: Emixustat vs placebo, Outcome 5: Mean change in lesion size from baseline at day 90 measured by FFA (mm²)



Analysis 1.6. Comparison 1: Emixustat vs placebo, Outcome 6: Mean change in lesion size from baseline at day 90 measured by CFP (mm²)



Analysis 1.7. Comparison 1: Emixustat vs placebo, Outcome 7: Incidence of CNV onset

Study or Subgroup	Emixustat		Placebo		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
SEATTLE Study	13	366	7	133	100.0%	0.67 [0.28 , 1.66]	
Total (95% CI)		366		133	100.0%	0.67 [0.28 , 1.66]	
Total events:	13		7				
Heterogeneity: Not applicable Test for overall effect: Z = 0.86 (P = 0.39) Test for subgroup differences: Not applicable							

Comparison 2. Fenretinide vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Progression of geographic atrophy (median; mm ² /year)	1		Other data	No numeric data
2.2 Incidence of CNV onset	1	245	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.26, 0.98]

Analysis 2.1. Comparison 2: Fenretinide vs placebo, Outcome 1: Progression of geographic atrophy (median; mm²/year)

Progression of geographic atrophy (median; mm²/year)

Study	Intervention	Median	Standard deviation	Number of participants
Mata 2013	Fenretinide 100 mg	2.14	1.66	45
	Fenretinide 300 mg	1.95	1.22	41
	Placebo	2.03	1.24	56

Analysis 2.2. Comparison 2: Fenretinide vs placebo, Outcome 2: Incidence of CNV onset

Study or Subgroup	Fenretinide		Placebo		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Mata 2013	15	163	15	82	100.0%	0.50 [0.26 , 0.98]	
Total (95% CI)		163		82	100.0%	0.50 [0.26 , 0.98]	
Total events:	15		15				
Heterogeneity: Not applicable Test for overall effect: Z = 2.03 (P = 0.04) Test for subgroup differences: Not applicable							

ADDITIONAL TABLES

Table 1. Adverse events reported for emixustat

Study number	Study name	Ocular adverse events	Systemic adverse events	Serious adverse events	Mortality
1	Dugel 2015	<p>50 emixustat participants (93%) and 5 placebo participants (28%) experienced at least 1 ocular AE. The most commonly reported ocular AE were:</p> <ul style="list-style-type: none"> • Chromatopsia (57.4% emixustat vs 16.7% placebo) • Delayed dark adaptation (48.1% emixustat vs 5.6% placebo) • Visual impairment (25.9% emixustat vs 5.6% placebo) • Blurred vision (14.8% emixustat vs 5.6% placebo) • Visual field defect (14.8% emixustat vs 0% placebo) <p>Dose-dependent pattern was observed for chromatopsia (33% in 2 mg emixustat arm, increasing to 83% in the 10 mg arm) and delayed dark adaptation (25% in 2 mg emixustat arm, increasing to 83% in 10 mg emixustat arm). All adverse events leading to emixustat discontinuation were ocular, with chromatopsia and delayed dark adaptation most common. Most ocular AE in both emixustat and placebo arms were considered to be related to study drug (chromatopsia in 30/31 emixustat participants and 3/3 placebo participants; delayed dark adaptation in 25/26 emixustat participants and 0/1 placebo participant).</p> <p>It was reported that majority of ocular AE (approximately 85%) resolved during study or within 7-14 days after study drug discontinuation.</p> <p>- Chromatopsia (56 events reported in 31 emixustat and 3 placebo participants)</p> <p>"Date of resolution available for 53 events: 29 events (54.7%) resolved before the end of dosing while 24 events (45.3%) resolved at or after the end of dosing."</p> <p>-Delayed dark adaptation (30 events reported in 26 emixustat and 1 placebo participant)</p> <p>"Date of resolution available for 26 events: 6 events (23.1%) resolved before the end of dosing while 20 events (76.9%) resolved at or after the end of dosing."</p>	<p>31 emixustat participants (57%) and 12 placebo participants (67%) experienced systemic AE. The most commonly reported systemic AE were:</p> <ul style="list-style-type: none"> • Headaches (9% emixustat vs 6% placebo) • Urinary tract infection (7% emixustat vs 0% placebo) • Dizziness (6% emixustat vs 6% placebo) • Nausea (6% emixustat vs 6% placebo) <p>"Most were considered by the investigator to be unrelated to the study drug". No dose-dependent pattern was observed.</p>	<p>3 emixustat participants experienced serious AE.</p> <ul style="list-style-type: none"> • Hospitalisation for COPD exacerbation (1 participant receiving 2 mg emixustat) • Chromatopsia occurred while driving (1 participant receiving 5 mg qAM and 1 participant receiving 5 mg qPM) <p>All AE subse-</p>	None reported

Table 1. Adverse events reported for emixustat (Continued)

				requently resolved.	
2	SEATTLE Study	<p>335 emixustat participants (90.5%) and 106 placebo participants (79.7%) experienced an ocular AE. The most commonly reported AE were:</p> <ul style="list-style-type: none"> • Delayed dark adaptation (55.4% emixustat vs 9.8% placebo) • Chromatopsia (17.6% emixustat vs 3% placebo) • Visual impairment (15.4% emixustat vs 14.3% placebo) • Erythrospia (14.6% emixustat vs 4.5% placebo) <p>These AEs were considered to be treatment-related. Incidence of the above AE was higher in participants assigned to the higher emixustat dose groups (5 mg and 10 mg) than the 2.5 mg group. More ocular AE (26%) than systemic AE (7%) led to study discontinuation among the emixustat participants. The most common ocular AE that led to study discontinuation was delayed dark adaptation, which had a dose-dependent pattern (6% in emixustat 2.5 mg; 15.1% in emixustat 5 mg and 21.4% in emixustat 10 mg).</p> <p>Decrease of LL-BCVA letter score ≥ 15 letters was more common in emixustat-treated participants after 12 months. The incidence was 19.7% (50/254) among emixustat participants and 9.4% (11/117) in the placebo arm. A dose-dependent response was observed. The incidence was 15.2% (15/99) in the 2.5 mg group, 20.6% (20/97) in the 5 mg group and 25.9% (15/58) in the 10 mg group. The incidence in emixustat-treated participants became comparable to the placebo arm after treatment ended. The incidence was 15.6% (56/360) in the emixustat arm and 15.6% (19/133) in the placebo arm at the last post-baseline measurement.</p>	<p>73% of emixustat participants experienced systemic AE compared to 85% of placebo participants. The most commonly reported systemic AE were:</p> <ul style="list-style-type: none"> • Fall (9.7% emixustat vs 15.8% placebo) • Nasopharyngitis (9.2% emixustat vs 20.3% placebo) • Hypertension (7.6% emixustat vs 12.8% placebo) • Urinary tract infection (4.6% emixustat vs 13.5%) • Diarrhoea (3.2% emixustat vs 11.3% placebo) • Peripheral oedema (2.4% emixustat vs 10.5% placebo) 	<p>77 (20.8%) emixustat participants and 30 (22.6%) placebo participants experienced serious AE.</p>	<p>6 participants died (all assigned to the emixustat cohort) due to non-ocular events considered by the investigator to be unrelated to the study drug.</p>

Table 2. Adverse events reported for fenretinide

Study number	Study name	Ocular adverse events	Systemic adverse events	Serious adverse events	Mortality
1	Mata 2013	<p>The most commonly reported ocular AE were:</p> <ul style="list-style-type: none"> • Reduced visual acuity (71.2% fenretinide vs 69.5% placebo) • Delayed dark adaptation (39.3% fenretinide vs 29.3% placebo) • Visual disturbance^a (25.2% fenretinide vs 7.3% placebo) • Blurred vision (7.36% fenretinide vs 2.4% placebo) • Dry eye (5.52% fenretinide vs 3.7% placebo) • Increased lacrimation (5.52% fenretinide vs 0% placebo) • Conjunctivitis (3.07% fenretinide vs 0% placebo) <p>Dose-dependent pattern was observed for delayed dark adaptation (37.5% in 100 mg cohort; 41% in 300 mg cohort), visual disturbance (18.8% in 100 mg cohort; 31.3% in 300 mg cohort)</p>	<p>Only systemic AEs that led to study withdrawal were reported.</p> <p>Only "skin and subcutaneous" disorders (rash and pruritus) were considered to be drug-related systemic AEs. 5 events were reported in the combined fenretinide arm while</p>	<p>"No statistically significant differences in the magnitude of delayed dark adaptation among the 3 treatment cohorts" based on</p>	<p>None reported</p>

Table 2. Adverse events reported for fenretinide (Continued)

mg cohort), blurred vision (6.3% in 100 mg cohort; 8.4% in 300 mg cohort), increased lacrimation (3.8% in 100 mg cohort; 7.2% in 300 mg cohort) and conjunctivitis (1.3% in 100 mg cohort; 4.8% in 300 mg cohort). All events of visual disturbance resolved shortly after drug cessation. It was not reported if delayed dark adaptation resolved after drug cessation.	no events were reported in the placebo arm.	responses to the validated Night Vision Questionnaire.
Ocular AEs (11 events) was more common than systemic AEs (5 events) in leading to study discontinuation in the combined fenretinide arm. Delayed dark adaptation, visual disturbance and reduced visual acuity were the most common ocular AEs leading to study discontinuation.		

^a Visual disturbance was described as "transient pattern of colour or darkened areas within their visual field upon waking or during an immediate exposure to bright light".

APPENDICES

Appendix 1. CENTRAL search strategy

fenretinide or fenofibrate or emixustat or A1120 or ACU-4429 or ALK-001 or visual cycle inhibitor or visual cycle modulator or RBP4 antagonist in Record Title AND geographic atrophy or macular degeneration or AMD or AMRD or maculopathy in Title Abstract Keyword

Appendix 2. MEDLINE Ovid search strategy

1. (macular degeneration or maculopathy or AMD or ARMD or geographic atrophy).tw.
2. exp Macular Degeneration/
3. exp Geographic Atrophy/
4. 1 or 2 or 3
5. exp *Enzyme Inhibitors/
6. retinol binding protein*.mp.
7. (fenretinide or fenofibrate or emixustat or A1120 or ACU-4429 or ALK-001).mp.
8. (visual cycle adj3 (inhibit* or modulat*)).mp.
9. RBP4 antagonist*.tw.
10. 5 or 6 or 7 or 8 or 9
11. 4 and 10
12. randomized controlled trial.pt.
13. controlled clinical trial.pt.
14. (random* or trial or group* or masked or control or placebo).tw.
15. 12 or 13 or 14
16. 11 and 15
17. geographic atrophy.m_titl.
18. random*.tw.
19. 13 or 18
20. 17 and 19
21. 16 or 20
22. Animals/
23. Humans/
24. 22 not 23
25. 21 not 24
26. (letter or comment or editorial).pt.
27. 25 not 26
28. limit 27 to yr="2005 -Current"

Appendix 3. Embase Ovid search strategy

1. (macular degeneration or maculopathy or AMD or ARMD or geographic atrophy).tw.
2. exp Macular Degeneration/
3. exp Geographic Atrophy/

4. 1 or 2 or 3
5. (macular degeneration or maculopathy or AMD or ARMD or geographic atrophy).tw.
6. exp Macular Degeneration/
7. exp Geographic Atrophy/
8. 5 or 6 or 7
9. exp *Enzyme Inhibitors/
10. retinol binding protein*.mp.
11. (fenretinide or fenofibrate or emixustat or A1120 or ACU-4429 or ALK-001).mp.
12. (visual cycle adj3 (inhibit* or modulat*)).mp.
13. RBP4 antagonist*.tw.
14. 9 or 10 or 11 or 12 or 13
15. 8 and 14
16. controlled clinical trial/
17. randomized controlled trial/
18. (random* or trial or group* or masked or control or placebo).tw.
19. 16 or 17 or 18
20. 15 and 19
21. geographic atrophy.m_titl.
22. random*.tw.
23. 21 and 22
24. 20 or 23
25. (letter or editorial).pt.
26. 24 not 25
27. animal/
28. human/
29. 27 not 28
30. 26 not 29
31. limit 30 to yr="2005 -Current"

Appendix 4. Web of Science Core Collection

TITLE: (fenretinide or fenofibrate or emixustat or A1120 or ACU-4429 or ALK-001 or visual cycle inhibitor or visual cycle modulator or RPB4 antagonist) AND TOPIC: (geographic atrophy or macular degeneration or AMD or AMRD or maculopathy)

Appendix 5. SCOPUS search strategy

TITLE (fenretinide OR fenofibrate OR emixustat OR "A1120" OR "ACU-4429" OR "ALK-001" OR "visual cycle inhibitor" OR "visual cycle modulator" OR "RPB4 antagonist") AND TITLE-ABS-KEY (geographic AND atrophy OR macular AND degeneration OR amd OR amrd OR maculopathy))

Appendix 6. ARVO web site

fenretinide OR fenofibrate OR emixustat OR "A1120" OR "ACU-4429" OR "ALK-001"

Appendix 7. ClinicalTrials.gov search strategy

Searched with keywords: fenretinide OR fenofibrate OR emixustat OR "A1120" OR "ACU-4429" OR "ALK-001"

Appendix 8. WHO ICTRP search strategy

Searched with keywords: fenretinide OR fenofibrate OR emixustat OR "A1120" OR "ACU-4429" OR "ALK-001"

Appendix 9. Data on study characteristics

Mandatory items	Optional items
Methods	
Study design	Exclusions after randomisation
<ul style="list-style-type: none"> • Parallel group RCT <i>i.e. people randomised to treatment</i> • Within-person RCT <i>i.e. eyes randomised to treatment</i> • Cluster RCT <i>i.e. communities randomised to treatment</i> • Cross-over RCT 	Losses to follow-up

(Continued)

	<ul style="list-style-type: none"> Other, specify 	Number randomised/analysed
Eyes or	<ul style="list-style-type: none"> One eye included in study, specify how eye selected Two eyes included in study, both eyes received same treatment, briefly specify how analysed (best/worst/average/both and adjusted for within person correlation/both and not adjusted for within person correlation) and specify if mixture one eye and two eye Two eyes included in study, eyes received different treatments, specify if correct pair-matched analysis done 	How were missing data handled? e.g., available case analysis, imputation methods
Unit of randomisation/ unit of analysis		Reported power calculation (Y/N), if yes, sample size and power
		Unusual study design/issues

Participants

Country		Setting
Total number of participants	<i>This information should be collected for total study population recruited into the study. If these data are only reported for the people who were followed up only, please indicate.</i>	Ethnic group
Number (%) of men and women		Equivalence of baseline characteristics (Y/N)
Average age and age range		
Inclusion criteria		
Exclusion criteria		

Interventions

Intervention (n =)	<ul style="list-style-type: none"> Number of people randomised to this group 	
Comparator (n =)	<ul style="list-style-type: none"> Drug (or intervention) name Dose 	
See MECIR 65 and 70	<ul style="list-style-type: none"> Frequency Route of administration 	

Outcomes

Primary and secondary outcomes as defined in study reports	List outcomes Adverse events reported (Y/N)	Planned/actual length of follow-up
See MECIR R70	Length of follow-up and intervals at which outcomes assessed	

Notes

Date conducted	Specify dates of recruitment of participants mm/yr to mm/yr	Full study name: (if applicable)
Sources of funding		Reported subgroup analyses (Y/N)
Declaration of interest		Were trial investigators contacted?
See MECIR 69		

HISTORY

Protocol first published: Issue 10, 2018

Review first published: Issue 12, 2020

CONTRIBUTIONS OF AUTHORS

All the authors contributed to and approved the final manuscript.

JLY: drafted the full review and drew the diagrams in the manuscript (the latter based on drawings previously produced by NL).

EL, JLC: wrote the methodology section (except the literature search strategy) and reviewed the final manuscript.

JLY, NL: identified eligible studies and undertook data extraction.

PR: created the literature search strategy.

NW, NL: conceived the project, provided input to the writing of the review and proofread the final manuscript.

DECLARATIONS OF INTEREST

JLY: none known

EL: none known

JLC: none known

PR: none known

NW: none known

NL: none known

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were outcomes identified in included RCTs that we did not have in our protocol, including mean change in geographic atrophy lesion size (mm²) and incidence of CNV in study/fellow eye (we were planning to assess incidence of geographic atrophy and neovascular AMD only in prevention studies including people with early or intermediate AMD). We did not include mean change in geographic atrophy lesion size (mm²) as reported by [Dugel 2015](#) in our outcome 'progression of geographic atrophy (mm²/year)' as we felt that the 90-day study period was insufficient to assess progression, given that geographic atrophy is a slow disease process. We included the incidence of CNV onset in our review as it was presented in two of the included trials. Both suggested a potential benefit of emixustat and fenretinide in lowering incidence of CNV. This finding, if confirmed in future trials, could have an important impact on patients and healthcare providers as well as in future AMD research.

Meta-analysis was not possible in the current systematic review as the reporting of visual and anatomical outcomes was not consistent among the identified trials, precluding us from pooling them. If there had been sufficient eligible studies, and no substantial clinical, methodological and statistical heterogeneity between them, we would have combined studies for meta-analysis and generated pooled estimates for each outcome using random-effects models. If there had been fewer than three studies in a given meta-analysis we would have used a fixed-effects model. In case of substantial statistical (I^2 value more than 60%) or clinical heterogeneity, we would have combined results in meta-analysis using a random-effects model if individual trial results were all consistent in the direction of the effect.